Synthesis and application of new chiral amines in Dutch resolution

Dalmolen, Jan

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Family Behaviour in Nucleation Inhibition

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The author wishes to gratefully acknowledge Professor Joe Gal from Denver for providing images of chirality-related stamps that can be seen at the cover of this thesis.

RIJKSUNIVERSITEIT GRONINGEN

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Family Behaviour in Nucleation Inhibition

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Prof. dr. H. Hiemstra
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voor mijn ouders en zus

Voorwoord

En dan is het tijd voor het voorwoord. Alhoewel deze zich altijd aan het begin van "het boekje" bevindt, wordt deze pas aan het eind geschreven. Zowel aan het eind van een periode van schrijven, als aan het eind van het gehele promotieonderzoek. Hoewel ik waarschijnlijk wel een heel hoofdstuk zou kunnen schrijven (misschien zelfs wel een heel boek!) van mijn tijd als promovendus, zal ik toch proberen dit enigszins binnen de perken te houden.

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Chapter 6 Nucleation Inhibition Studies in the Resolution of Chiral Acids

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Chapter 1
Introduction to Chirality & Resolutions

In this chapter an overview is given of the history of chirality and its consequences as well as some basic principles. Possible routes to enantiopure compounds are summarized. One of these routes, the preparation of enantiopure compounds by resolution, will be discussed in more detail. Dutch Resolution refers to the use of mixtures of structurally similar resolving agents (also called 'families'). This chapter also describes the aspects of the first generation, second generation and reverse Dutch Resolution, and the resemblances and differences between these and classical approaches. At the end of this chapter the aim and an outline of this thesis are given.

1.1 Basic Concepts of Chirality

In 1874, the French chemist Le Bel[1] and the Dutch chemist van't Hoff[2], independently postulated that the four chemical bonds that carbon atoms can form are directed to the corners of a tetrahedral structure (Figure 1.1). This discovery proved to be the cornerstone in the study of the three-dimensional structure of organic compounds, and developed to what now is commonly referred to as stereochemistry.

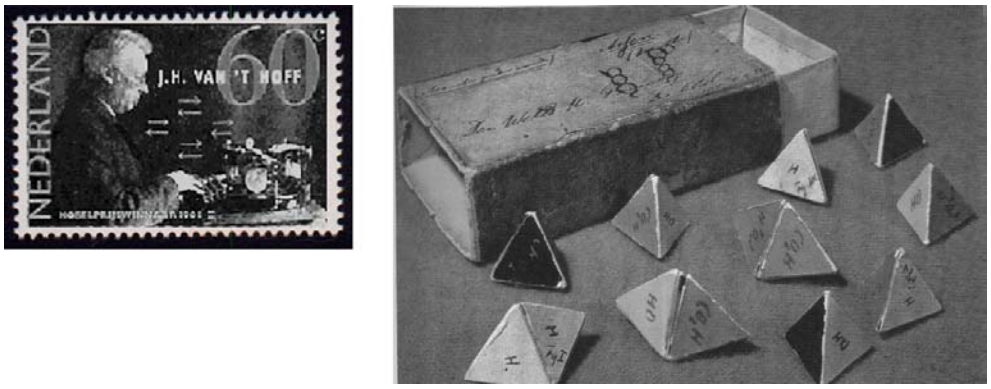


Figure 1.1 *Dutch stamp of Jacobus Henricus van't Hoff at work (left). Van't Hoff circulated his stereochemical ideas to his colleague chemists by sending them three-dimensional paper models of tetrahedral molecules (right).*

In general, carbon atoms that have four non-identical groups attached to them or molecules that are not superimposable on their mirror image are said to be asymmetric, or *chiral* (Greek; χειρ (cheir), meaning *hand*). These mirror images are called *enantiomers* (Figure 1.2). The word enantiomer is derived from the Greek εναντιος (enantios), which means *opposite*. A molecule that is superimposable on its mirror image is called *achiral*.

We constantly encounter chirality and chiral objects in daily life; for instance shoes, scissors, screws, and spiral staircases are all examples of chiral objects. Even in our body, all amino acids (except glycine) of every protein are almost always found as the same 'left-handed' enantiomers, whereas all sugars in DNA, RNA, and in the metabolic pathways, are 'right-handed'.

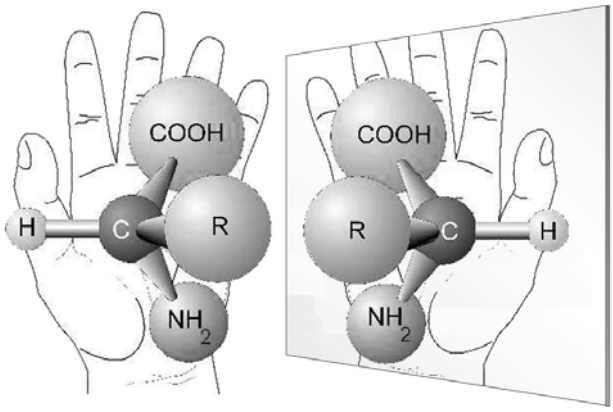


Figure 1.2 *Molecules or objects that are non-identical with their mirror image are said to be chiral. Furthermore, nearly all amino acids in the human body are left-handed.*

Compounds that have the same molecular formula but different bruto chemical structures are called *isomers.* The classification of isomers and their description is given in Figure 1.3.

Enantiomers belong to the first class of configurational stereoisomers, the so-called optical isomers.[3] In an achiral environment, all physical properties (*e.g.* melting points, boiling points, densities) of enantiomers are identical, except the direction they rotate plane-polarized light. If a solution of the optically active compound rotates the plane-polarized light clockwise (dextrorotatory), it is designated (+) or *d*. Therefore, a solution of the mirror image enantiomer must rotate the plane-polarized light in the opposite direction at the same magnitude, it is designated (–) or *l* (levorotatory). If only one enantiomeric form of a chiral molecule is present, it is called *enantiomerically pure* (or enantiopure). A mixture containing equal amounts of opposite enantiomers is a *racemate* and racemic solutions show no rotation of plane–polarized light. Racemates are frequently represented as (±).

Because enantiomers have identical physical properties, they cannot be directly separated by conventional methods (*e.g.* distillation, crystallization, chromatography on conventional stationary phases), but only be resolved by use of an optically pure (or enriched) chiral reagent.

There are molecules that also belong to the class of optical stereoisomers that are **not** mirror images of one another. These isomers are referred to as diastereoisomers (or shorter diastereomers), and contain more than one stereogenic center. As a general rule, for a molecule having n stereogenic centers, 2^n diastereomers are possible; this number is reduced to less than 2^n if *meso* forms, *i.e.* internal symmetry, of the molecule are possible. Diastereoisomers have different physical properties and therefore can be separated from one another by conventional methods.

Epimers are a special category of diastereomers. They are a pair of stereoisomers with more than one stereogenic center that differs in chirality at one and only one chiral center. A chemical reaction, which causes an interconversion in chirality at one of these chiral centers, is called an epimerization.

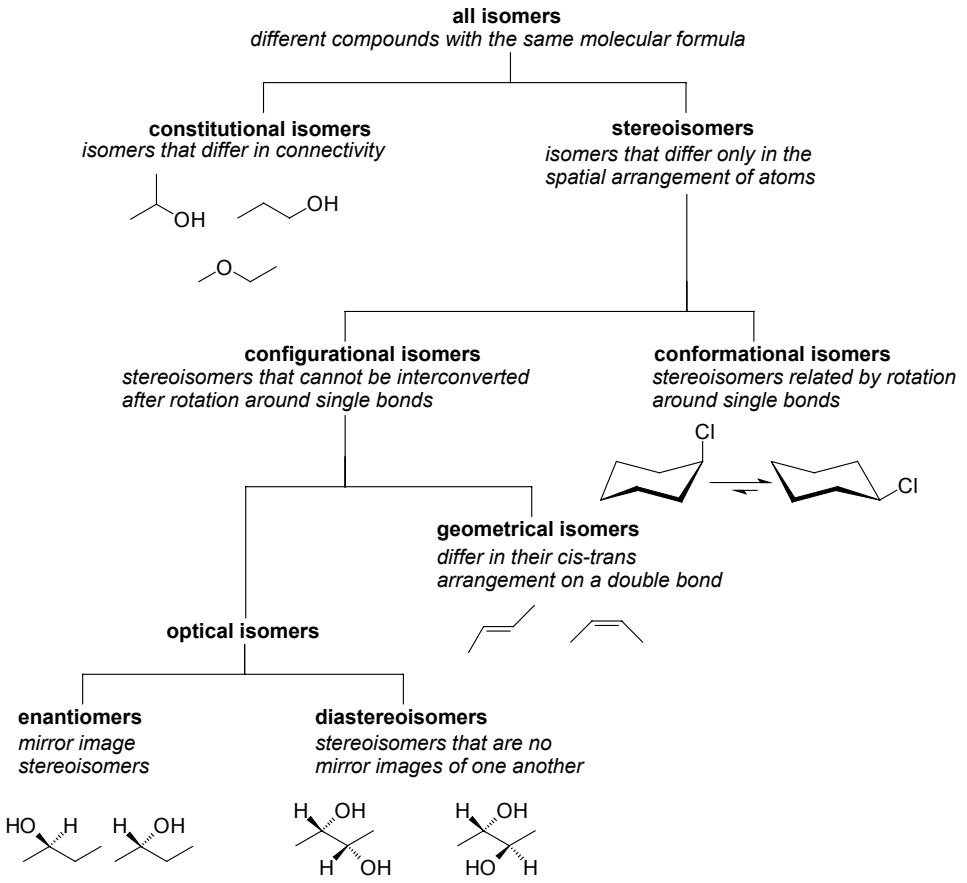


Figure 1.3 *The relationship between different kinds of isomers.*

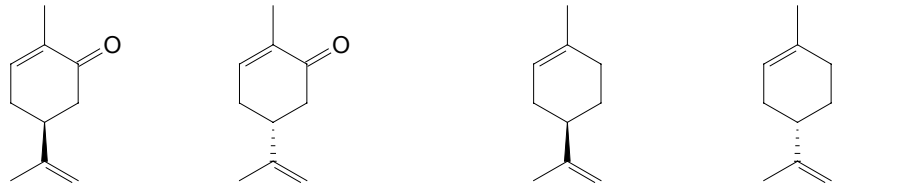
Stereoisomers differ in the way their atoms are arranged in space, whereas constitutional isomers, the class into which all others fall, differ in the order in which atoms are bonded together.

1.2 Chirality and Bioactivity

Although enantiomers have the same physical properties, in a chiral environment, for example that of living organisms, enantiomers can show different chemical behaviour due to different chiral discrimination (diastereomeric interactions).[4] Both carvone and limonene (Figure 1.4) provide classic examples of how enantiomerism can lead to different interactions in the human body. The enantiomers of these two odourants have different scents owing to a different 3-D fit on an odour receptor and/or on different odour receptors.[5]

(*S*)-Carvone is a naturally occurring ketone that can be found in caraway seeds, and is used in the perfume industry and as a flavouring spice. (*R*)-Carvone is found in mint leaves. The typical spearmint and caraway odours are those of mirror molecules; caraway is the 'right-handed' enantiomer **1.1** and spearmint is the 'left-handed' enantiomer **1.2**.[6]

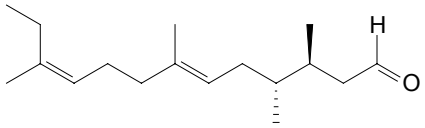
Orange and lemon peels both contain limonene. However, the limonene molecule in orange peel is the (–)-enantiomer **1.3**, and the one in the lemon is the (+)-enantiomer **1.4**. And as we all know, these spatially different structures have different odours.



(*S*)-(+)-Carvone **1.1** *(caraway)* (*R*)-(-)-Carvone **1.2** *(spearmint)* (*R*)-(-)-Limonene **1.3** *(orange)* (*S*)-(+)-Limonene **1.4** *(lemon)*

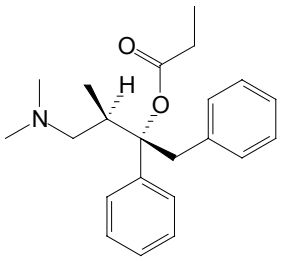
Figure 1.4 *Enantiomers of carvone and limonene and their corresponding odours.*

Similarly, chirality plays a role in the chemical communication in nature. Faranal is an insect trail pheromone of the pharaoh's ant (*Monomorium pharaonis*).[7] When a worker ant finds some food source of interest to the colony it leaves a trail of faranal which other workers pick up and follow. Only the (3*S*,4*R*)-(+)-faranal **1.5** is the bioactive enantiomer (of four stereoisomers).

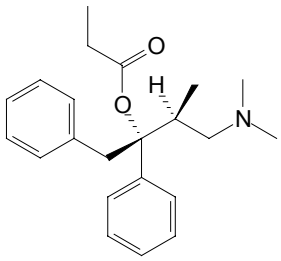


(3*S*,4*R*)-(+)-Faranal **1.5**

One can imagine that the different bioactivity of enantiomers is of utmost importance in the manufacturing of pharmaceuticals; there are many examples where the stereoisomers used in drugs show differences. In the literature, the more active isomer for a given action is often referred to as the *eutomer*, whereas the other is called the *distomer*.[8] The distomer can exhibit an undesirable side effect, show no serious side effect or even have independent biological activities.[9] Examples of the latter are both enantiomers of propoxyphene, since they have independent therapeutic value. Dextropropoxyphene **1.6** (Darvon) is marketed as a painkiller, whereas the antipode levopropoxyphene **1.7** (Novrad) is a cough suppressant. Note how the mirror image relationship is reflected in their trade names.[10]



(*R*)-(+)-Propoxyphene **1.6**
(Darvon)



(S)-(-)-Propoxyphene **1.7**
(Novrad)

Figure 1.5 *The enantiomers of propoxyphene exhibit useful but different biological activities.*

In general, even if the distomer shows no unwanted side effects, it must be regarded as isomeric ballast and therefore the preparation of enantiopure drugs is preferred.

1.3 Routes to Enantiomerically Pure Compounds[11,12]

In the quest for enantiopure compounds, there are three primary sources to choose from (Figure 1.6):

- The rich diversity of enantiopure compounds from the chiral pool,
- Stereoselective conversion of prochiral substrates (asymmetric synthesis), and
- Resolution of a racemate into its pure enantiomers.

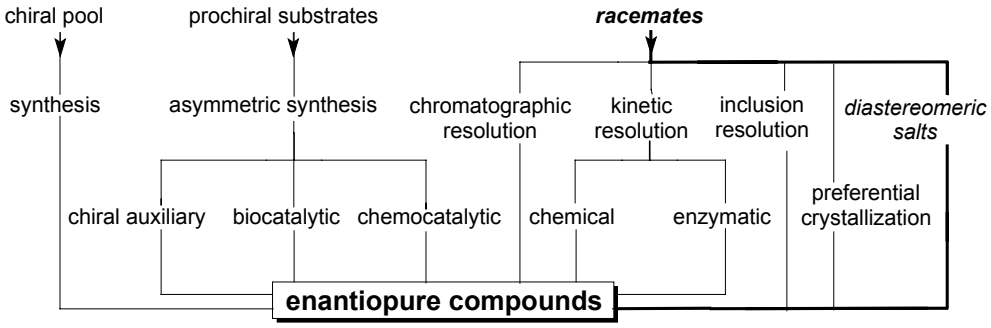
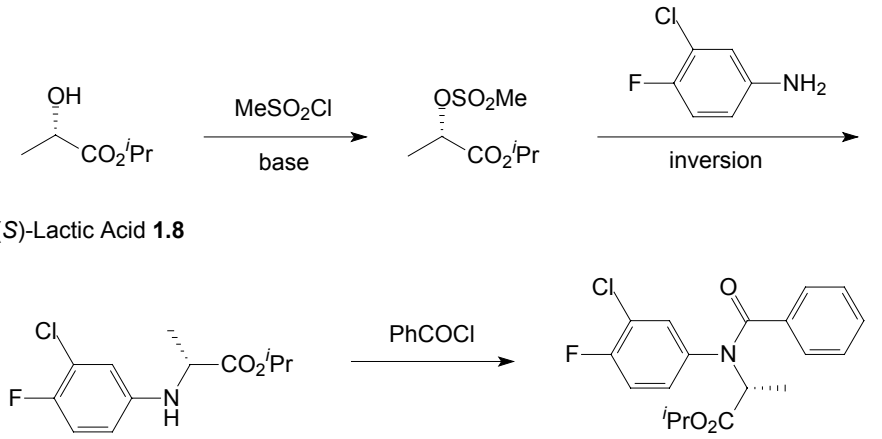


Figure 1.6 *Routes to enantiomerically pure compounds.*

These three main routes (and their sub-routes) will be described briefly in the next few sections illustrated by several examples from the literature.

1.3.1 Chiral Pool[13]

The chiral pool consists of enantiomerically pure or highly enriched starting materials derived from natural resources, such as amino acids, carbohydrates, hydroxy acids, alkaloids and terpenes. If such a precursor is available, then it is often the most cost-effective way of introducing asymmetry.[14] An example of using the chiral pool is the synthesis of the herbicide (*R*)-flamprop-*iso*propyl starting from one of the oldest and most well known chiral hydroxy acids, L-lactic acid **1.8**.[15] After conversion to the mesylate, a single inversion step leads to the desired final product with the (*R*)-configuration (Scheme 1.1).



Scheme 1.1 *The synthesis of enantiopure herbicide **1.9** from L-lactic acid **1.8**.*

1.3.2 Prochiral Substrates

A potential synthesis component (synthon) is prochiral if in one reaction step a new stereogenic center is created; although this reaction can entail sub-steps (like hydrolysis of an intermediate). This reaction step can be, for example, an addition to a double bond in the molecule (*e.g.* prochiral olefins), or substitution of one of two enantiotopic groups (*e.g.* prochiral diols).

1.3.2.1 Chiral Auxiliaries[16]

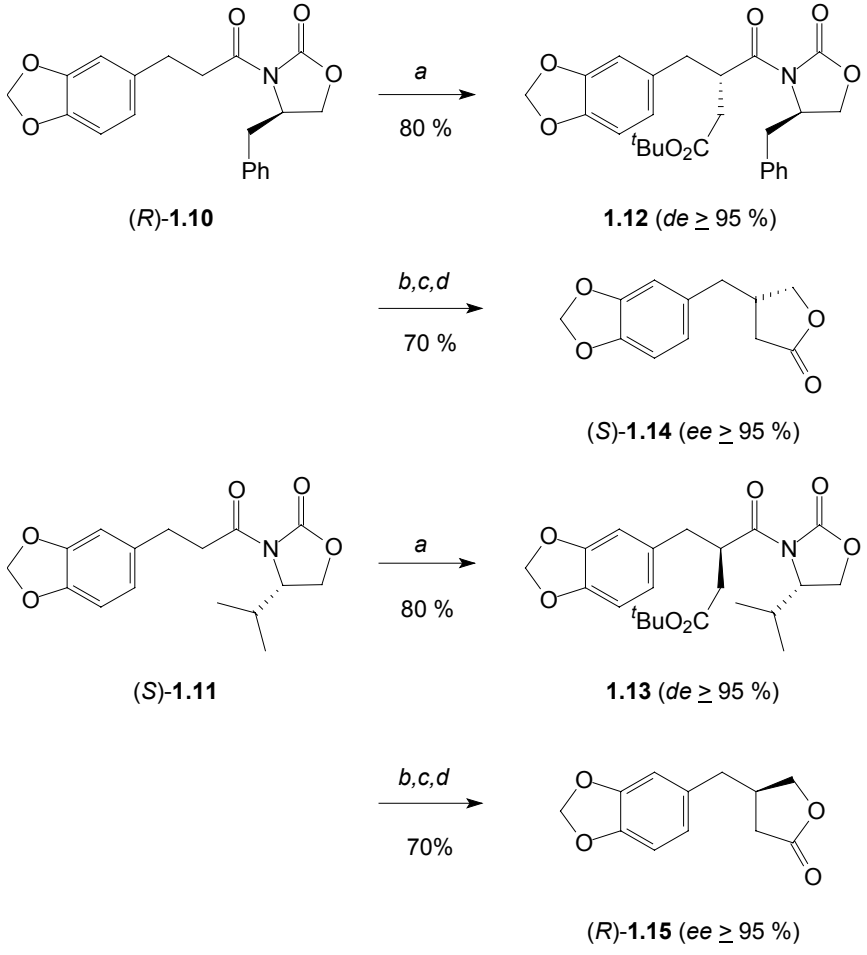
The first strategy in asymmetric synthesis involves the use of a chiral auxiliary. In this strategy the temporary introduction of a chiral group to a prochiral substrate influences the outcome of the reaction that produces the new stereogenic center. It is preferable that both enantiomers of the chiral auxiliary are available so that it is possible to prepare both enantiomers of the final products if desired.

Once the chiral auxiliary has achieved its purpose, it can, at least in ideal situations, be removed from the molecule and re-used. Therefore the ideal chiral auxiliary should be easy to recover without any loss of enantiomeric purity. If in the removal step the chiral center of the chiral auxiliary is destroyed (immolative removal), the chiral auxiliary cannot be recycled. In this case, in the literature reference is sometimes made to a “chiral template” rather than chiral auxiliary.

One of the most well-known chiral auxiliaries in the literature are the chiral oxazolidinones applied in the Evans methodology.[17] A demonstration of the use of oxazolidinones as an effective chiral auxiliary is in the synthesis of key butyrolactone intermediates for the

lignans gossypifan and savinin (hibalactone) (Scheme 1.2).[18] The key step in this sequence was a highly diastereoselective alkylation of an *N*-acyloxazolidinone enolate.

Commercially available (4*R*)-benzyl and (4*S*)-isopropyl-2-oxazolidinones were *N*-acylated with dihydrocinnamic acid to give *N*-acyloxazolidinones (*R*)-**1.10** and (*S*)-**1.11.** Diastereoselective alkylation with *tert*-butylbromoacetate gave in each case predominantly one diastereomer (**1.12** and **1.13**, respectively) (*de* ≥ 95 %). After removal of the oxazolidinone moiety, the crude acid was reduced to the corresponding primary alcohol with BH_3.THF, and then converted into a lactone using TFA to afford the desired benzylbutyrolactones **1.14** and **1.15**.



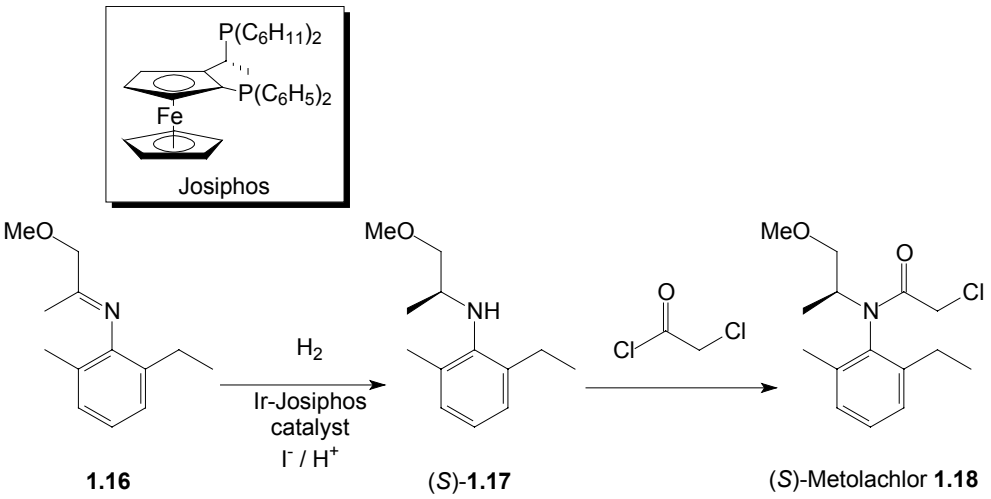
Scheme 1.2 *Asymmetric synthesis of butyrolactones **1.14** and **1.15**. Reagents and conditions: (a) NaHMDS, $BrCH_2CO_2{}^tBu$; (b) LiOH, H_2O_2; (c) BH_3.THF; (d) TFA.*

Another example of the use of chiral auxiliaries will be described in Chapters 3 and 4 of this thesis; enantiomerically pure (*R*)-phenylglycine amide proved to be an excellent chiral auxiliary in the preparation of enantiopure 1-aryl-1-butylamines and 1-aryl-3-butenylamines. These amines are valuable synthons in the preparation of biologically active compounds and will be used in Dutch Resolution experiments (as described in Chapters 5–7).

1.3.2.2 Chemocatalysis

Asymmetric chemocatalysis is a rapidly developing area, as researchers look for new ligands and catalysts derived therefrom that are more active, more selective, and more broadly applicable to bring about enantioselective reactions.

An example of the largest-scale enantioselective catalytic process at present (a capacity of more than 10,000 tons per year) is the production of (*S*)-Metolachlor **1.18**, an important herbicide used on farmland for the control of grass weeds in row crops (*e.g.* corn and soybean).[19] Of the four stereoisomers, only the two (*S*)-diastereomers show biological activity. The key step in the technical process is the asymmetric hydrogenation of imine intermediate **1.16** by using iridium complexed to a ferrocenyl diphosphine ligand known as Josiphos (Scheme 1.3) followed by a chloroacetylation of (*S*)-**1.17**.



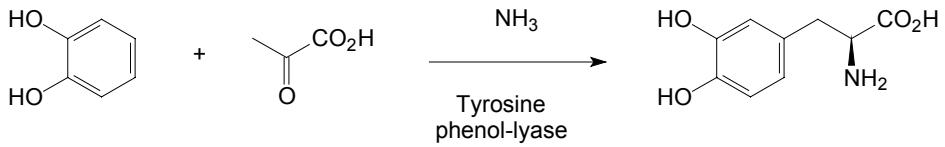
Scheme 1.3 *The process for the industrial production of (S)-Metolachlor **1.18**.*

This catalytic process has an exceptionally high efficiency. Under a hydrogen pressure of 80 bar and a reaction temperature of 50 °C, satisfactory enantiomeric excesses (79 % *ee*) and a turnover number of more than 1,000,000 can be achieved.[19c]

1.3.2.3 Biocatalysis[20]

Biological processes are usually regulated by enzymes. For instance, the digestion of food is catalyzed by enzymes. Biocatalysts used in synthetic organic chemistry include natural enzymes and unnatural modifications produced by, for example site-specific mutagenesis or gene shuffling. These systems have the potential to catalyze reactions of specific substrates with high enantio- and stereospecificity. Among the enzymes used, lipases have demonstrated a great versatility in enzymatic hydrolysis, transesterification, or aminolysis reactions. Other biocatalysts, for example lyases,[21] have been reported for the production of pharmaceutically interesting L-amino acids.

Tyrosine phenol-lyase (TpL) is used in the production of (*S*)-3,4-dihydroxyphenylalanine (L-DOPA), utilized in the treatment of Parkinson's disease and which is a precursor to the neurotransmitter dopamine. In the industrial one-pot three-component process, catechol **1.19**, pyruvic avid **1.20** and ammonia are combined in a reactor in the presence of intact cells from the *Erwinia herbicola* containing the TpL-biocatalyst (Scheme 1.4).[19b,22]



catechol **1.19** pyruvic acid **1.20** L-DOPA **1.21**

Scheme 1.4 *Production of L-DOPA **1.15** using tyrosine phenol-lyase.*

The volumetric productivity of this process is up to 110 $g.L^{-1}$. Over half the market need of about 250 tons of L-DOPA is produced by this enzymatic method involving TpL.[22a]

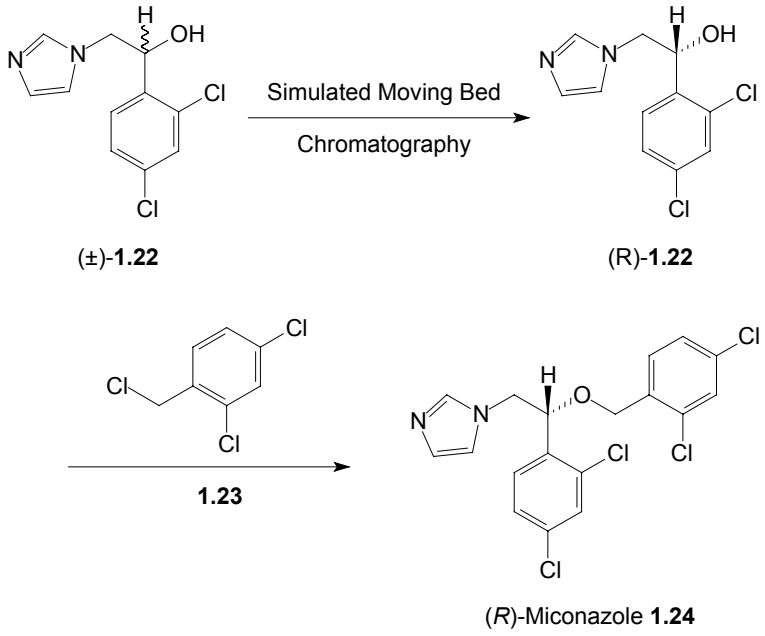
1.3.3 Starting from the Racemate – Resolutions[12,23]

If a chemical reaction is performed in the laboratory with achiral starting materials and under achiral conditions, the products can be chiral but will be formed as a racemic mixture of two enantiomers. To obtain enantiopure or enantio-enriched materials, a resolution step is required. The most frequently used resolution methods will be outlined below. Another resolution method, the resolution by preferential crystallization (entrainment), will be discussed in the Chapter 2. Section 1.5 of this Chapter will deal with a relatively new technology in the field of classical resolution, referred to as Dutch Resolution, since this method will be an important constituent of this thesis.

1.3.3.1 Chromatographic Resolution

The use of chromatographic techniques in the resolution of enantiomers to obtain significant quantities of enantiomerically pure drugs and drug intermediates is a growing field of interest. Chromatographic separation relies on a difference in affinity between the (chiral) stationary phase and a mobile phase (the solvent moving through the stationary phase, the eluent). Simulated moving bed (SMB) chromatography is a continuous chromatographic multi-column separation process wherein six to eight columns are run in series. In recent years, SMB chromatography has become an alternative approach for the separation of enantiomers in quantities ranging from grams to several hundred kilograms.[24]

A successful example of SMB is in the commercial scale synthesis of enantiopure (*R*)-miconazole **1.24** from racemic intermediate **1.22**. Miconazole is used in the treatment of, for example, skin diseases and tuberculosis.



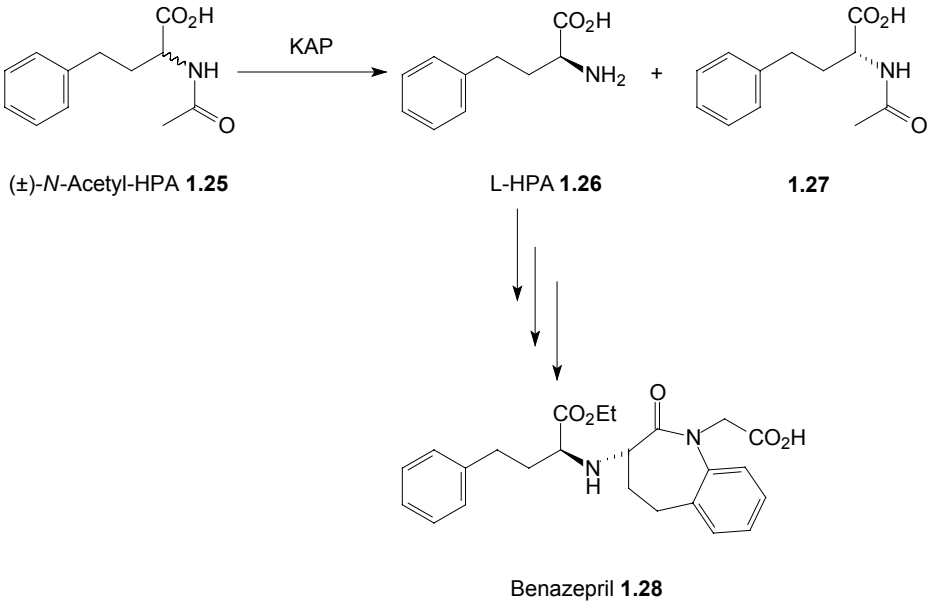
Scheme 1.5 *The preparation of single enantiomer (R)-miconazole **1.24** by SMB-chromatography.*

In the SMB process, intermediate (*R*)-**1.22** is separated and after a substitution reaction with 2,4-dichlorobenzyl chloride **1.23**, (*R*)-miconazole **1.24** is obtained as the single enantiomer. Unfortunately, the non-desired enantiomer could not be re-racemized.[19c]

1.3.3.2 Kinetic Resolution[25]

In a kinetic resolution process, one of the two enantiomers of the racemate is converted to another compound. Because there is a difference in the rate of conversion of either enantiomer, the starting material will be enriched in the slowest converted enantiomer if the reaction is stopped before completion. This difference in rate is induced by chemical catalysts or biocatalysts like enzymes. When the unwanted enantiomer is racemized *in situ* during the reaction, a 100 % theoretical yield of the enantiopure product can be reached, and the process is referred to as *dynamic* kinetic resolution.[26]

A nice example of enzymatic resolution is involved in the preparation of Benazepril **1.28**. Benazepril is one of the most potential angiotensin converting enzyme (ACE) inhibitors, which contain an L-homophenylalanine ethyl ester in their structure.[27] Recently, Regla *et al.* reported a new synthetic strategy for the synthesis of the homophenylalanine (HPA) intermediate **1.26** by enzymatic resolution.[28] Both enantiomers of **1.26** have potential application in the synthesis of ACE inhibitors. By using the kidney acetone powders (KAPs) derived from different mammalian species such as beef, dog, hog, rat, and sheep they were able to resolve racemic *N*-acetyl HPA **1.25** (Scheme 1.6). The beef kidney afforded the best results, providing the highest isolated yields, 41 % and 38 %, and enantiomeric excesses of > 99 % and 94 % for both L-HPA **1.26** and D-*N*-Acetyl-HPA **1.27**, respectively.

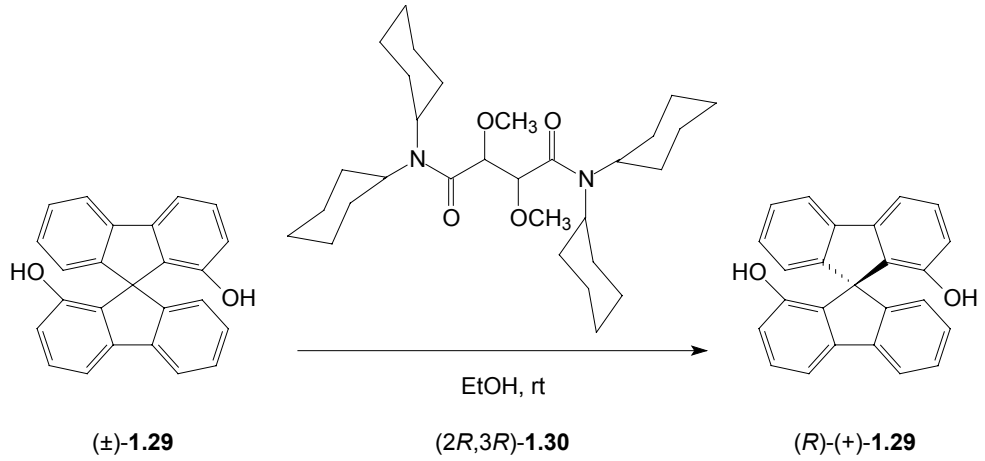


Scheme 1.6 *Enzymatic resolution of (±)-Acetyl-HPA **1.25** with mammalian KAP in the synthesis towards Benazepril **1.28**.*

1.3.3.3 Inclusion Resolution[29]

A relatively new field in the resolution of racemates is inclusion resolution[30] which is based on chiral discrimination and recognition in the crystalline phase. A chiral host molecule forms an inclusion complex preferably with one of the enantiomers by forming hydrogen bonds. The most widely applied chiral host molecules are the derivatives of tartaric acid,[31,32,33] succinamide[34] and lactic acid.[30a]

Recently,[35] both enantiomers of 9,9'-spirobifluorene-1,1'-diol (SBIFOL) **1.29** were conveniently obtained by inclusion resolution with 2,3-dimethoxy-*N*,*N*,*N'*,*N'*-tetracyclohexylsuccinamide **1.30** (Scheme 1.7). Diol **1.29** provides potential backbones for chiral ligands in asymmetric catalysis and finds a place in molecular electronics,[36] light-emitting materials[37] and other areas.[38] Racemic diol **1.29** and (2*R*,3*R*)-**1.30** were mixed in a 1:1 molar ratio in ethanol at room temperature (rt). After a few minutes, the crystalline complexes were collected by filtration, and after liberation, (*R*)-(+)-**1.29** was obtained in 43 % yield (of the maximum possible 50 % yield) in an enantiomeric excess of 80 %. By repeating the procedure of inclusion crystallization once, the enantiomeric excess of (*R*)-(+)-**1.29** was further increased to 99 %. The (*S*)-(–)-**1.29** enantiomer was obtained in 99 % *ee* by inclusion resolution using (2*S*,3*S*)-**1.30**.



Scheme 1.7 *Inclusion resolution of **1.29** with (2R,3R)-**1.30**.*

1.4 Classical Resolution by Diastereomeric Salt Formation

Despite methodologies like those just described, optical resolution via diastereomeric salt formation is still the most widely used method of preparing pure enantiomers.[12] In this section a historical overview is given and aspects that play a role in classical resolutions are discussed.

1.4.1 Louis Pasteur [39]

Tartaric acid ("acid of grapes") is a chiral dicarboxylic acid found in wine must. It is used in the food industry to give an acid taste, and as an antioxidant. The chirality of tartaric acid was discovered in 1832 by Jean-Baptiste Biot, who observed its ability to rotate polarized light.[40]

When Louis Pasteur repeated the work of Biot in 1847 as research practice,[41] he found that one of the isomers of tartaric acid consists of equal quantities of the levo- and dextro-forms. This optically inactive form is called *Racemic Acid* (Greek; racemus, which means *bunch of grapes*). The term 'racemic' originally referred to the origin of the acid (grapes), but nowadays in chemistry it refers to an equal mixture of opposite enantiomers.

By slow crystallization of a solution of the sodium ammonium salt of tartaric acid Pasteur obtained two types of colorless mirror image crystals (Figure 1.7). By using a magnifying glass and a pair of tweezers, he separated the crystals by hand. Equimolar solutions of these separated crystals showed equal but opposite optical activity. Even though this is the first reported resolution in the literature, one can imagine that this time-consuming 'crystal picking' is not very convenient in, for example, an industrial environment.

Figure 1.7 *French stamp of Louis Pasteur (left). Actual crystals of the 'right-handed' and 'left-handed' enantiomorphic forms of sodium ammonium tartrate (right).*

However, there was an element of luck in his (accidental) discovery. Pasteur performed his crystallization experiments on a cold day in May in the cool climate of Paris. If he would have conducted his experiments later that summer, he would not have made his revolutionary discovery for it was found that sodium ammonium tartrate only forms a *conglomerate* below 26 °C.[42] A conglomerate is a mixture of crystals of individual enantiomers that can, in principle, be separated mechanically.[43] Only approximately 10 % of the racemic compounds form conglomerates. The majority crystallizes as true racemates with an equimolar mixture of opposite enantiomers.

1.4.2 Diastereomeric Salt Formation

A more practical, and the most frequently applied method is the 'classical' resolution of racemates through formation and separation of diastereomeric salts. In this strategy, an acid-base reaction is involved between a racemate and a resolving agent, which is in practice an enantiopure (single) enantiomer. If the two diastereomeric salts that are formed differ in solubility, filtration can be used to separate the diastereomeric pair. The principle of classical resolution is depicted in Figure 1.8.[44] When you start with the racemate, depicted here as two mirror-image triangles and you associate them with a "chiral figure" (the resolving agent), for instance by salt formation, you obtain two non-mirror-image figures, related as diastereomers, which can be separated by conventional methods, like crystallization, chromatography or other physical manipulation.

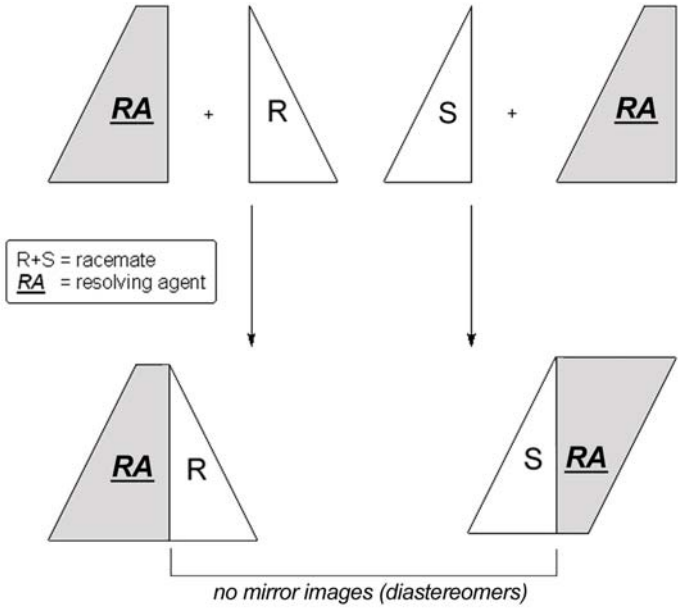


Figure 1.8 *Two dimensional representation of diastereomeric salt formation.*[44]

For instance, when the solubilities of the two salts (the more soluble and the less soluble salt) are very different, one of the salts is insoluble and can be filtered out of the mixture, leaving the other in solution (in the most ideal case). Finally, the salt is decomposed by treatment with either acid or base, and the resolving agent can be recovered.

An illustrative example of a classical resolution employed in an industrial process, is the diastereomeric crystallization of D-phenylglycine **1.32** from the racemate developed by

Andeno (now DSM Pharma Chemicals).[45] Optically pure **1.32** is an important intermediate in the production of semi-synthetic β-lactam antibiotics. Racemic **1.32** is easily obtained from a Strecker reaction on benzaldehyde **1.31** followed by hydrolysis of the nitrile (Figure 1.9).

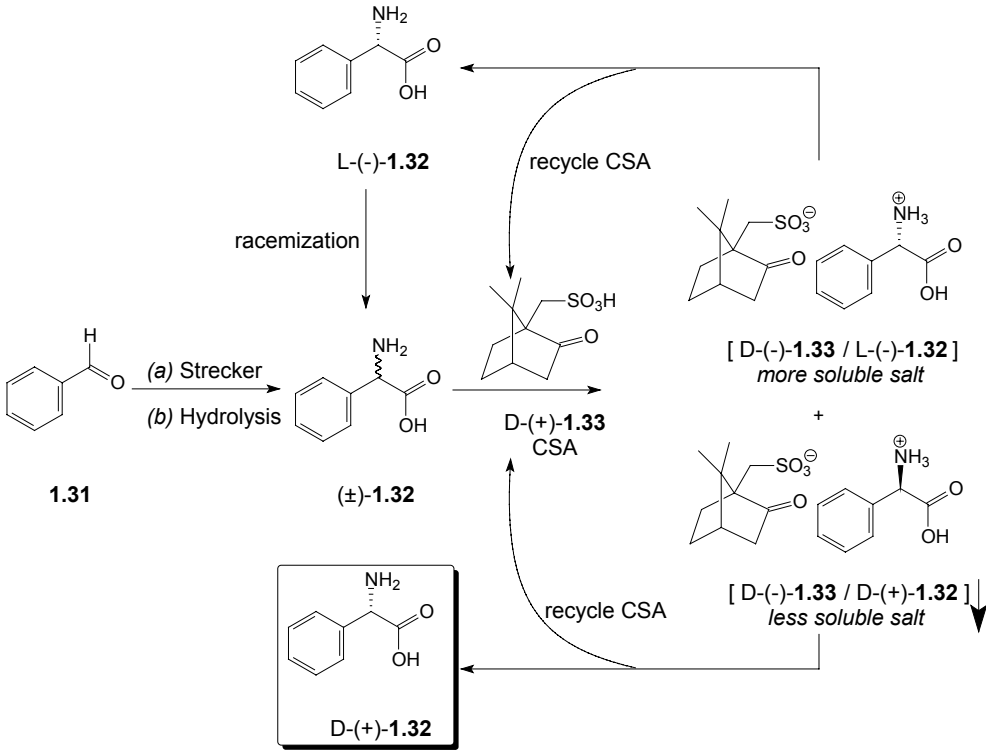


Figure 1.9 *DSM process for D-phenylglycine **1.32**.*

The racemate could be successfully resolved with optically pure D-(+)-camphorsulfonic acid **1.33** (CSA) as the resolving agent in aqueous medium; the more soluble diastereomeric salt is D-(–)-**1.33**/L-(–)-**1.32** and the less soluble diastereomeric salt is the D-(–)-**1.33**/D-(+)-**1.32**. After precipitation the less soluble salt is isolated, the L-isomer is racemized in a separate step (after liberation) and can be re-used. This process is performed on more than a thousand tons scale *per annum*.

1.4.3 Commonly used Resolving Agents

For the separation of racemic acids naturally occurring alkaloids have been used like cinchonidine **1.34**, quinine **1.35**, cinchonine **1.36**, quinidine **1.37**, brucine **1.38**, strychnine **1.39,** dehydroabiethylamine **1.40** and ephedrine **1.41** (Figure 1.10). Also synthetic bases like 1-phenylethylamine **1.42** and amphetamine **1.43** have been employed in resolution experiments. The advantage of synthetic resolving agents like **1.42** and **1.43** is the (commercially) availability of both enantiomers.

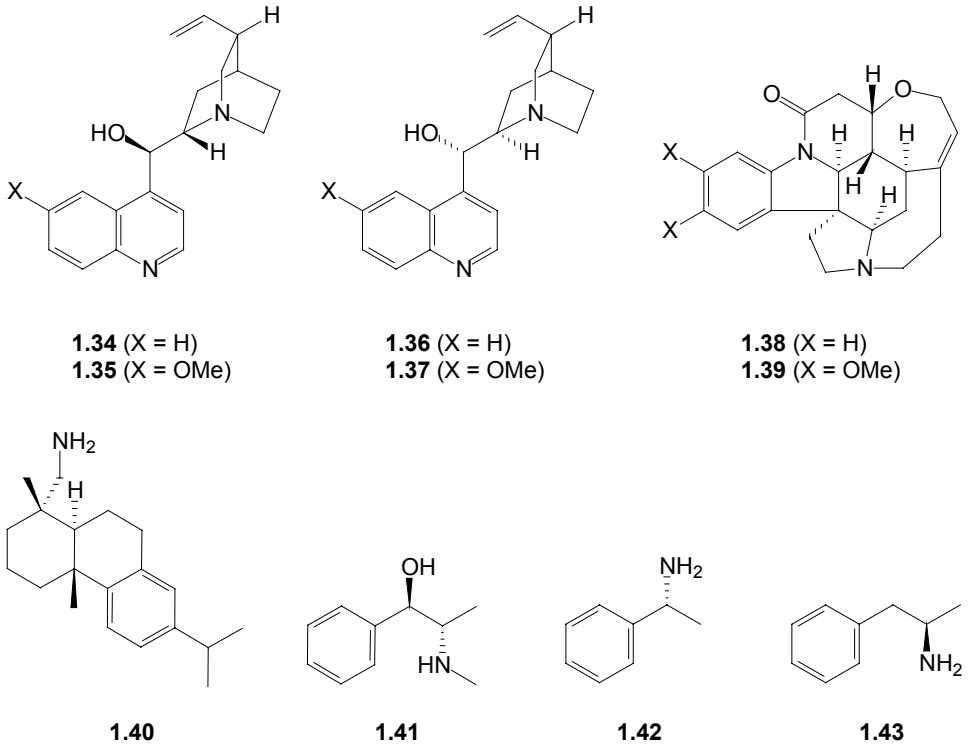
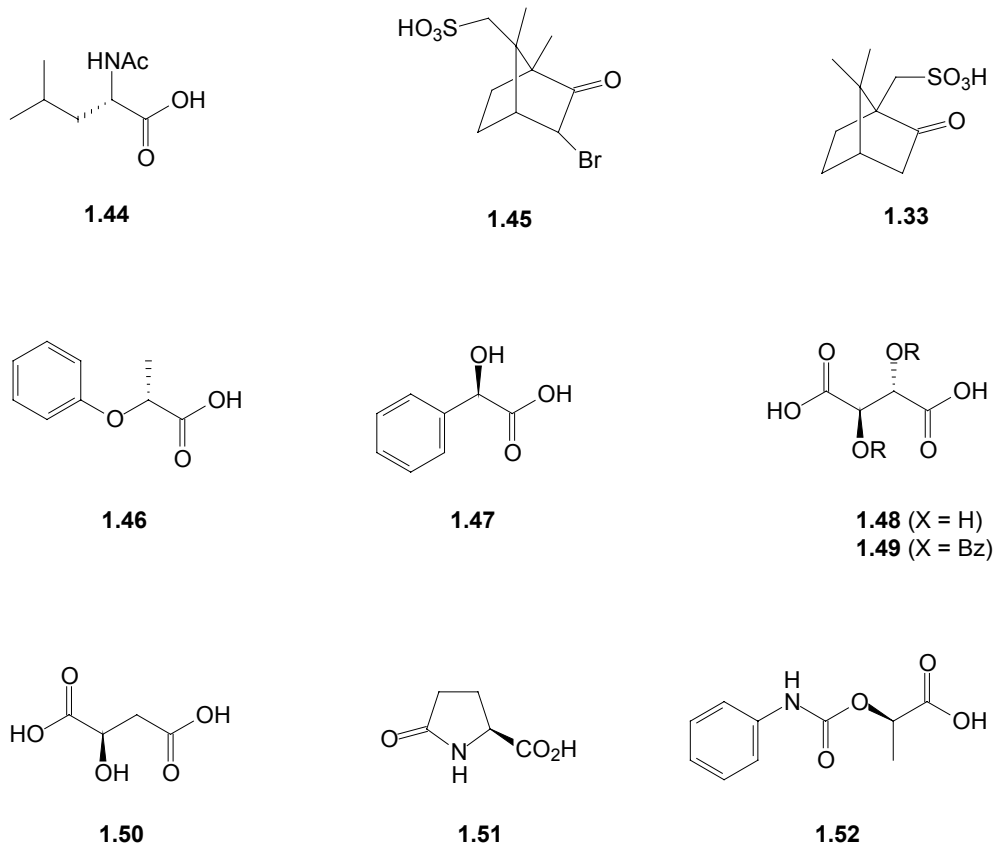


Figure 1.10 *Some commonly used basic resolving agents.*

Among the preparative methods used for obtaining enantio-enriched amines by resolution, there are procedures involving the use of acidic resolving agents like *N*-acetylleucine **1.44**, *α*-bromocamphor-*π*-sulphonic acid **1.45**, camphorsulfonic acid **1.33**, phenoxypropionic acid **1.46**, mandelic acid **1.47**, tartaric acid **1.48** and its dibenzoyl derivative **1.49,** malic acid **1.50** and pyroglutamic acid **1.51** (Figure 1.11). Also synthetic acids like L-phenylcarbamoyllactic acid **1.52** can be versatile resolving agents.[46] For instance, L-**1.52**

is used for the resolution of 1-(*p*-chlorophenyl)ethylamine, a key intermediate in the synthesis of a chiral fungicide.[47]



1.44 **1.45** **1.33**

1.46 **1.47** **1.48** (X = H)
1.49 (X = Bz)

1.50 **1.51** **1.52**

Figure 1.11 *Some commonly used acidic resolving agents.*

Finding a suitable resolving agent for a given substrate is not trivial. Trial-and-error and practical experience is still the best methodology since no sound theoretical basis is available. Despite many attempts, neither computer-assisted modeling,[48] detailed examination of the crystal structure data of diastereomeric salts,[49] study of the energy differences of the two diastereomeric salts,[50] nor empirical correlations[51] have made it possible to predict an appropriate resolving agent that has to be used. If a resolution process is available for a certain compound, this method does not necessarily work for other substrates with closely related structures.

1.5 Dutch Resolution

Since the original description by Pasteur in 1853,[52] the technique of resolutions by diastereomeric salt formation essentially remained unchanged. The crucial step in the development of a resolution procedure is to find a suitable resolving agent. As mentioned earlier in this chapter, selecting a suitable resolving agent to resolve a substrate of interest has been trial-and-error, guided by the experience of the experimenter, and is sometimes as much art as science.

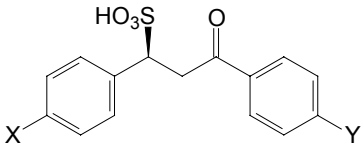
In 1998, a new approach to classical resolution was reported whereby, instead of using one resolving agent, mixtures of structurally closely related resolving agents (so-called *families* of resolving agents) were added to the racemic mixture. This method was coined "Dutch Resolution",[53] a name which has been widely adopted. Dutch Resolution certainly has something of combinatorial characteristics in it; upon the simultaneous addition of a family of resolving agents, higher *de* values of the first salts were obtained via this method. Success rates were 90–95 %, in general on testing only a few families of resolving agents, compared to the usual 20–30 % estimated.[23b]

1.5.1 First Generation Dutch Resolution

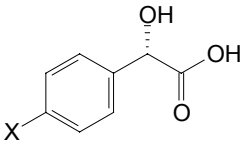
Examples of various enantiopure families of acidic and basic resolving agents (and their abbreviations) that are currently available are shown in Figure 1.12. Families based on substituted chalcone sulphonic acids **1.53** (J-mix), mandelic acids **1.54** (M-mix), dibenzoyltartaric acids **1.55** (T-mix), cyclic phosphoric acids **1.56** (P-mix), 1-phenylethylamine **1.57** (PE-I-mix), **1.58** (PE-II-mix), **1.59** (PE-III-mix) and the family bases on 1,2-aminoalcohols **1.60** (PG-mix) are available. Note how these homochiral families differ only on the position or nature of the substituent. However, the PE-III mix constitutes of family members in which the alkyl side-chain is varied. With these families many resolutions have been carried out readily whereas with single resolving agents resolutions were either poor or failed.

In practice, three structurally related resolving agents are used in a 1:1:1 ratio. A mixture of these resolving agents is usually found in the first isolated salts, but in non-stoichiometric ratios. Two typical examples of Dutch Resolution are shown in Scheme 1.8 and Scheme 1.9 and more examples can be found in the original Dutch Resolution article.[53a]

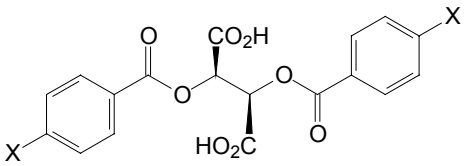
DL-*threo*-(4-methylthiophenyl)serine amide **1.61** could be successfully resolved by using 1 mol equivalent of the family of cyclic phosphoric acids **1.56**, the P-(–)-mix.[54] In this case, a diastereomeric pure salt precipitated containing the desired (2*S*,3*R*)-enantiomer in 99 % enantiomeric excess (*ee*) (Scheme 1.8, entry 4). The precipitated salt contains all three of the individual family members in a non-stoichiometric ratio. This solid solution behaviour of the resolving agents is observed in many cases of Dutch Resolution experiments. Note that each of the individual family members of the P-(–)-mix give salts with moderate *ee*'s (entries 1–3) and in two of the three cases the enantiomer with the opposite configuration is isolated. (entries 1 and 2).



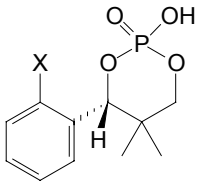
1.53 (J-Mix)
X = H, Me, Cl
Y = H, Me, Cl



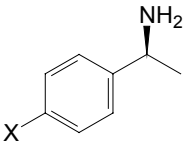
1.54 (M-Mix)
X = H, Br, Me, Ph



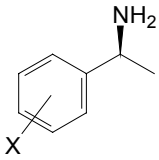
1.55 (T-Mix)
X = H, Me, OMe



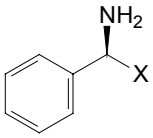
1.56 (P-Mix)
X = H, Cl, MeO



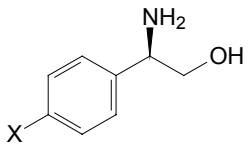
1.57 (PE-I-Mix)
X = H, Br, Me



1.58 (PE-II-Mix)
X = H, *o*-NO_2, *p*-NO_2

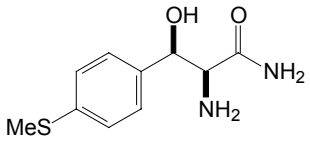


1.59 (PE-III-Mix)
X = CH_3, C_2H_5, $CH(CH_3)_2$

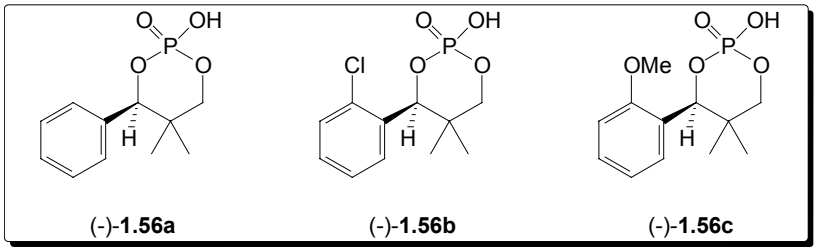


1.60 (PG-Mix)
X = H, Me, OMe

Figure 1.12 *Families of resolving agents.*



DL-**1.61**



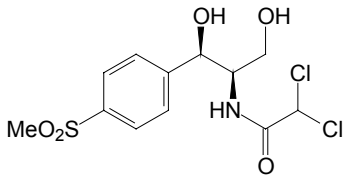
(-)-**1.56a** (-)-**1.56b** (-)-**1.56c**

Entry	Resolving Agent	Yield (%)	*ee* (%)	S-Factor[a]	Mix-ratio in salt
1	(–)-**1.56a**	47	52 (2*R*,3*S*)	0.49	–
2	(–)-**1.56b**	55	17 (2*R*,3*S*)	0.19	–
3	(–)-**1.56c**	41	67 (2*S*,3*R*)	0.55	–
4	(–)-P-Mix (1:1:1)	25	99 (2*S*,3*R*)	0.49	**1.56a**:**1.56b**:**1.56c** (12:35:53)

[a] S = 2 × yield × *de*.[§]

Scheme 1.8 *Dutch Resolution of DL-threo-(4-methylthiophenyl)serine amide* ***1.61*** *with the P-(–)-Mix.*

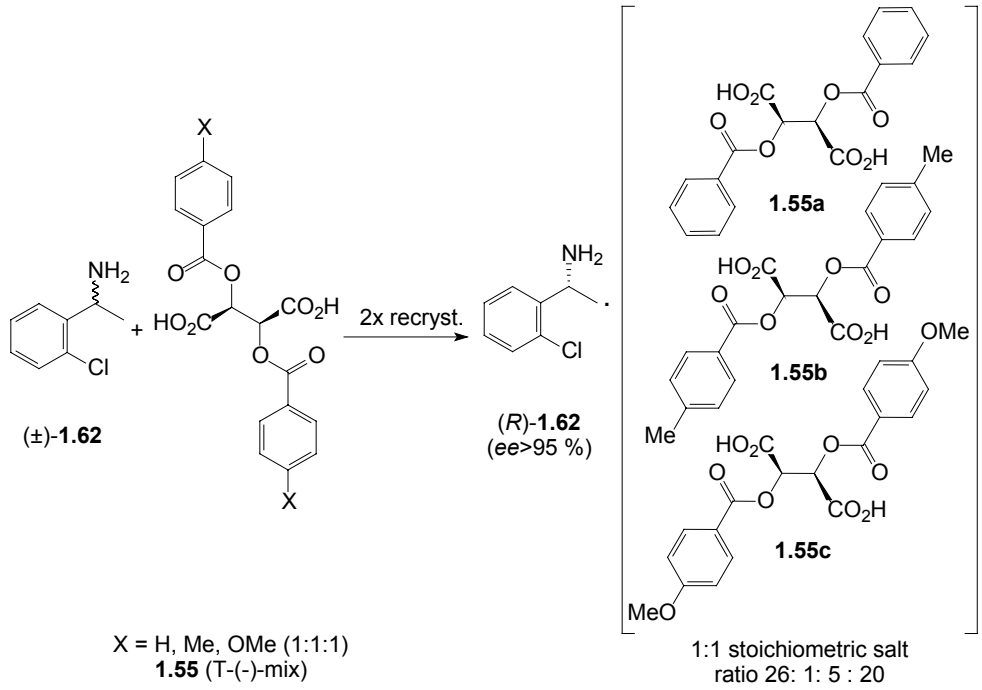
The resolved phenyl serine amide can be used as an intermediate in the synthesis of thiamphenicol,[55] which is an antimicrobial substance used for the treatment of infectious diseases in cattle, pigs and poultry.



Thiamphenicol

[§] *The S-factor is a measure for the resolution efficiency and is described in section 1.6.2 of this chapter.*

On use of the family based on the dibenzoyltartaric acids **1.55** (T-(–)-mix) it was possible to resolve DL-2-(2-chlorophenyl)ethylamine **1.62**. After two recrystallizations from ethanol a salt is obtained with > 95% *ee* and contains the three family members of the T-mix in a 1:5:20 ratio (Scheme 1.9). Note how phenyl- and the tolyl-substituted family members **1.55a** and **1.55b** are incorporated in the salt only to a small extent.



Scheme 1.9 *Dutch Resolution of DL-1-(2-chlorophenyl)ethylamine **1.62** with the T-(–)-mix.*

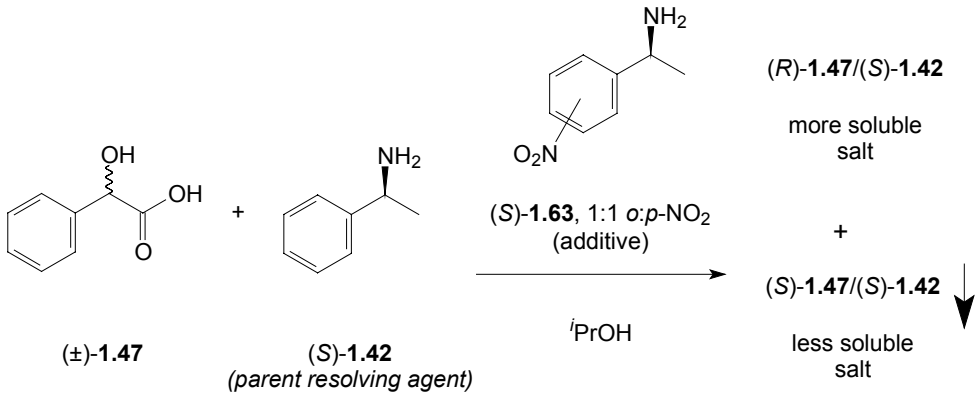
1.5.2 Second Generation Dutch Resolution

In all reported cases of the *Angewandte* article,[53a] the ratios of the separate resolving agents differed substantially from the originally stoichiometries. In 10 of the 46 cases, no detectable amount of at least one of the resolving agents was found in the first isolated salts; in three other cases one of the resolving agents was present in < 10 mol % in the salts. Further investigation has led to the observation that the resolutions proceed less well in the

absence of these non- or poorly incorporated resolving agents. The suspicion arose that these non-incorporated family members might be "the dog that didn't bark".[‡]

To put this idea to the test, a model system was designed with two family members. The resolving agent present in the highest fraction is called the 'parent resolving agent' and the other component present in the smallest fraction is the 'additive'. The additive is typically a poorly or non-incorporated resolving agent. This approach is referred to as 'second generation Dutch Resolution'.[56,57]

The case studied in most detail is the resolution of racemic mandelic acid **1.47** with (*S*)-1-phenylethylamine **1.42** as the parent resolving agent (Scheme 1.10).[56] In this system, the more soluble diastereomeric salt is (*R*)-**1.47**/(*S*)-**1.42** and the less soluble diastereomeric combination is the (*S*)-**1.47**/(*S*)-**1.42** salt. A 1:1 mixture of the *ortho*:*para*-substituted family members (S)-**1.63** was chosen as the additive, this mixture together with (*S*)-**1.42** forms the original PE-II-mix **1.58** (Figure 1.12). All experiments were performed at non-optimal conditions, so any improvement could be easily detected.



Scheme 1.10 *Second generation Dutch Resolution of racemic **1.47** with (S)-**1.42** in the presence of (S)-**1.63** as an additive.*

In the absence of the additive, the resolution of (±)-**1.47** with (*S*)-**1.42** delivered a first salt with a diastereomeric excess (*de*) of 14 % and S-factor of 0.19 (Table 1.1, entry 1). When 10 mol % of (*S*)-**1.42** is substituted by a 1:1 mixture of *ortho*:*para* nitro-substituted (*S*)-1-

[‡] *In "Silver Blaze"* (1984), *Sir Arthur Conan Doyle's fictional hero Sherlock Holmes once solved a case because a dog that would have been **expected** to bark did not. Worded differently, "often, what is most important is what is not said". This metaphor was first used by Dr. J. W. Nieuwenhuijzen.*[56b]

phenylethylamine **1.63**, the *de* of the first isolated salt increased from 14 % to 55 % and the S-factor increased to 0.41 (entry 2). No detectable amount of either *ortho*- or *para*-(*S*)-**1.63** was found in the precipitated salt.

Table 1.1 *Second generation Dutch Resolution of racemic **1.47** with (S)-**1.42** in the absence and presence of (S)-**1.63** as an additive.*

Entry	Resolving Agent	Additive	Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[c]
1	(*S*)-**1.42**	–	–	68	14	0.19
2	(*S*)-**1.42**	(*S*)-**1.63**	10	37	55	0.41

[a] Isolated yield of the first salt. [b] *de* of the first isolated salt. [c] S = 2 × yield × *de*.

Crystallizations in the presence of (*S*)-**1.63** were observed to begin at a lower temperature than with (*S*)-**1.42** alone. With the aid of turbidity measurements it was established that this mixture of nitro-derivatives functioned as an effective *nucleation inhibitor*.[†] For both the diastereomeric salts, nucleation inhibition was observed. By suppressing the nucleation of the more soluble diastereomer, higher resolvability can be obtained. Turbidity measurements will be described in more detail in Chapter 6.

This second generation Dutch Resolution provides an ideal resolution protocol because:

- It was found that resolutions in the presence of (S)-**1.63** give high *de* values even at a higher concentration. The use of higher concentrations is particularly attractive for industrial applications, since in one batch more material can be resolved.
- The efficiency of the resolution can be enhanced by adding a sub-stoichiometric amount of a family member which acts as a nucleation inhibitor and is **not** incorporated. A pure salt is obtained, which after liberation of the enantio-enriched substrate affords only a single resolving agent. This is of evident benefit in recycling the resolving agent.

This second generation Dutch Resolution protocol was also used in the resolution of racemic *meta*-nitrophenylbutylamine with the family of the cyclic phosphoric acids **1.56** and is described in chapter 4.4 of this thesis.

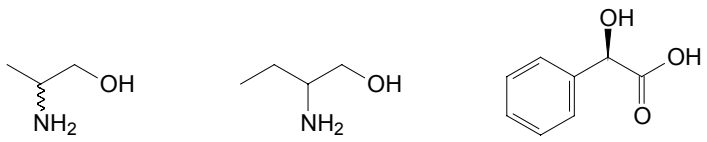
[†] *For a more detailed description of a nucleation inhibitor see Chapter 2.8.*

1.5.3 Reverse Dutch Resolution

The methodology just described can also be performed in a reverse manner, *i.e.* a family member of the racemate is added instead of a compound structurally related to the resolving agent. An example is the resolution of alaninol **1.64** in the presence of an enantiopure family member 2-amino-1-butanol **1.65** (Figure 1.13). Whereas the latter amine **1.65** can be successfully resolved with **1.47**, the resolution of **1.64** with mandelic acid itself provides salts with low *de* values. In the absence of **1.65**, the resolution of (±)-**1.64** with (*R*)-**1.47** delivered a first salt with a *de* of 13 % and S-factor of 0.11 (Table 1.2, entry 1).[54]

When racemic **1.64** is partly substituted by (*R*)-**1.65** a mixed salt co-crystallizes containing both (*R*)-alaninol **1.64** and (*R*)-2-aminobutanol **1.65**. Depending on the starting ratio of **1.64** and **1.65** more or less of the (*R*)-alaninol is incorporated in the first isolated salts (entries 2–4. Best results were obtained with (*S*)-**1.65** as the additive; on addition of 33 mol % of (S)-**1.65** a salt crystallizes which contained almost no additive. One subsequent recrystallization provided the desired enantiopure (*R*)-alaninol. Most likely, the (*S*)-family member of the racemate stereoselective hinders the crystallization of the non-desired (*S*)-**1.64**/(*R*)-**1.47** diastereomer.*

Figure 1.13 and Table 1.2 *Reverse Dutch Resolution of (±)-alaninol **1.64** with (R)-mandelic acid **1.47** using (R)- or (S)-2-amino-1-butanol **1.65** as a family member.*



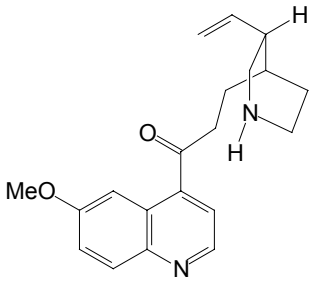
(±)-**1.64** (*R*)- or (*S*)-**1.65** (*R*)-**1.47**

Entry	Starting ratio		Yield	*de*	S	Mix-ratio in salt	
	1.64 (%)	**1.65** (%)	(%)	(%)	Factor	**1.64** (%)	**1.65** (%)
1	100	–	43	13	0.11	–	–
2	50	50 (*R*)	38	94	0.71	25	75
3	75	25 (*R*)	34	92	0.63	57	43
4	90	10 (*R*)	37	88	0.65	76	24
5	67	33 (*S*)	24	94	0.45	98	2

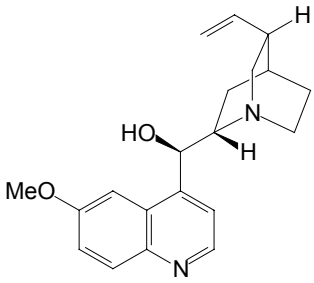
* *Unpublished results B. Kaptein, DSM Research.*

1.5.4 Reexamination of Pasteur's Work

In 1853 Pasteur reported the synthesis of optically active quinotoxine (**1.66**), a degradation product of quinine (**1.35**).[52b,58] He used alkaloid **1.66** as a resolving agent to perform the first ever resolution by diastereomeric salt formation. By treating racemic tartaric acid **1.48** with (+)-quinotoxine, Pasteur was able to precipitate preferentially the salt containing (+)-tartaric acid/(+)-quinotoxine, whereas the (–)-tartaric acid/(+)-quinotoxine salt remained in solution.



(+)-Quinotoxine **1.66**



Quinine **1.35**

Since Pasteur obtained degradation product quinotoxine by a rearrangement reaction induced by mild treatment of quinine with sulfuric acid, it is not improbably that there was still a small quantity of starting material **1.35** present in the isolated end-product **1.66**. Quinine is a perfect potential family member of quinotoxine, and this exactly fulfills the second generation Dutch Resolution protocol as described in Chapter 1.5.2. If quinine acts as a family member and suppresses the nucleation of the more soluble salt, the high stereoselectively in the precipitation process might be possibly due to nucleation inhibition.

Even today, the work of Pasteur still receives much attention. Recently, his work on the morphology of sodium ammonium tartrate was reexamined by Nakazaki and coworkers.[59] In our view, a simple experiment well worth trying is reexamination of the resolution of racemic tartaric acid with quinotoxine in the absence and presence of quinine by performing turbidity measurements.

1.6 Parameters for Evaluation

1.6.1 Enantiomeric- and Diastereomeric Excess

For a mixture of enantiomers or diastereomers, where the compositions are given as *A* and *B* (and $A + B = 1$), respectively the enantiomeric excess (*ee*) and the diastereomeric excess (*de*) are defined as:

$$ee\ (\%) = 100 \times \left(\frac{\mathrm{A - B}}{\mathrm{A + B}} \right) \qquad de\ (\%) = 100 \times \left(\frac{\mathrm{A - B}}{\mathrm{A + B}} \right)$$

Hence in a 1:1 (racemic) mixture of the enantiomeric pairs, the *ee* is 0 %.

In chiral HPLC, for instance, by integration of the peak areas the enantiomeric- or diastereomeric excesses can be calculated.

In reactions where enantio- or diastereo*selectivity* plays a role, it is preferable to use the terms enantiomeric ratio (*er*) or diastereomeric ratio (*dr*) to make clear the percentage of one enantiomer or diastereomer in a mixture relative to that of the other:

$$er = A : B \qquad dr = A : B \quad (\text{and } A + B = 100)$$

By using a polarimeter, the enantiomer recovered can be identified by verifying the direction the plane-polarized light is rotated. By comparing the magnitude (and direction) to known experimental results, the optical purity (in %) can be determined:

$$\%\ \text{optical purity} = 100 \times \frac{[\alpha]_{\text{mixture}}}{[\alpha]_{\text{pure sample}}}$$

In this formula, the *specific rotation* $[\alpha]$ is defined as:

$$[\alpha]_{\lambda}^{\mathrm{T}} = \frac{\alpha}{c \times l}$$

in which α is the observed rotation (in °), l is the length of the cell (in decimeters) and c is the concentration used (in $g \cdot mL^{-1}$). Since usually a cell of 1 decimeter in length and several milligrams are weighed in a 10 mL flask, the formula can be rewritten as:

$$[\alpha]_{\lambda}^{T} = 10{,}000 \times \frac{\alpha}{w}$$

in which w is the amount of sample in milligrams in a 10 mL flask. The specific rotation should always be defined together with the concentration (c), the solvent used, the wavelength of the polarized light (λ) and the temperature (T).

The optical purity corresponds to the enantiomeric excess since they both express the excess of one species over the other, *e.g.* an optical purity of 40 % corresponds to an *ee* of 40 %. (and thus an *er* of 70 :30)

1.6.2 Resolution Efficiency

The efficiency of a resolution experiment can be expressed in terms of the resolvability (S). The so called S-factor was introduced by Fogassy[60] and is used to compare resolution processes. It is calculated by multiplying the chemical yield by the diastereomeric excess (*de*) of the first obtained salt:

$$S = 2 \times \text{yield} \times de$$

A factor 2 is introduced to adjust for the fact that the theoretical yield cannot be higher than 50 % (or 0.50). The *de* of the first isolated salts can range between 0 and 100 % (or 1.0). Thereupon, the S-factor must range between 0 and 1, where 1 corresponds to complete separation.

The theoretical maximum resolution efficiency can be calculated on the basis of the solubilities of the diastereomeric salts (in $mol \cdot L^{-1}$), k_{more} and k_{less}, for a given solvent.

$$S_{max} \approx \frac{k_{more} - k_{less}}{k_{more}}$$

From this equation it can be seen that the greater the difference in solubility between the two diastereomeric salts, the higher the maximum S-factor that could be reached.

In a binary (melting) phase diagram, the lowest melting point corresponds to the *eutectic point* and the corresponding composition is the *eutectic composition*. When a resolution is performed under equilibrium conditions, the composition of the mother liquor corresponds to the maximum solubility.

From the composition at the eutectic point, the theoretical maximum resolution efficiency is defined as:

$$S_{max} = \frac{1 - 2\,x_{eut}}{1 - x_{eut}} = \frac{ee\ (\%)_{eut}}{50 - ee\ (\%)_{eut}}$$

where x_{eut} is the eutectic composition and the $ee\ (\%)_{eut}$ is the enantiomeric excess of the eutectic solution.[61] If the maximum S-factor is not obtained in a certain resolution process, it is most probable that the equilibrium has not been reached.

Moreover, binary phase diagrams allows calculation of the maximum yield (R_{max}):

$$R_{max} = \frac{0.5 - x_{eut}}{1 - x_{eut}} \times 100\ \% \qquad (R_{max} = 1 - 50\ \%)$$

1.7 Chiral Pool *versus* Asymmetric Synthesis *versus* Resolution

Each approach has its specific advantages and disadvantages, and all of these strategies are used both in industrial surroundings and in research laboratories.

Low cost and high enantiopurity are two reasons for considering ‘fishing’ in the chiral pool. A possible drawback of this approach is that most natural products are available in only one enantiomeric form.

The potential of catalytic asymmetric synthesis is reflected in the Nobel Prize in chemistry 2001 awarded to W.S. Knowles, R. Noyori and K.B. Sharpless.[62] In theory asymmetric synthesis, either by chiral auxiliaries or asymmetric catalysis, should be the most cost-effective method for producing single enantiomers since it has a theoretical yield of 100 %. However, this is frequently counterbalanced by the availability of only one enantiomer of the chiral auxiliary, high costs and unsuitable removal conditions of the chiral auxiliary (see also Chapter 3.1). Asymmetric catalysis is often hampered by the long time-to-market and expensive transition metals. Furthermore, even though only a small amount of catalyst is required, optimization of a catalytic process is a time-consuming process, since multiple parameters are involved (*e.g.* lengthy total syntheses of chiral ligands, solvent, temperature, catalyst loading and scale-up). Recently, the screening for suitable catalysts for a certain

process has changed drastically by the introduction of high-throughput experimentation (HTE).[63]

Even though the theoretical yield in resolution processes is 50 % starting from the racemate, if the unwanted isomer can find a profitable purpose or can be racemized *in situ*, this method becomes highly advantageous. Although the resolution technique still is far from predictable, it has the advantage that it is a relatively simple procedure, which can often quickly be incorporated into an industrial process. In the fine chemical industry it is therefore still one of the most frequently applied methods.[12,14]

1.8 Aim and Outline of this Thesis

Improvements in resolutions are not only important for industrial applications, but it is also very important to gain more insight in the resolution process. The main focus of this thesis is threefold;

a. The development of a new family of basic resolving agents based on a new synthetic strategy.

b. The use of these materials, either single or as families in Dutch Resolution experiments.

c. The use of these materials to understand the family behaviour in nucleation inhibition.

Since the possible success of Dutch Resolution lies most probably in the phenomenon of 'nucleation inhibition', it is therefore important to understand what is going on at the molecular level during the crystallization process of the diastereomeric salts. Therefore, a short introduction to the basic principles of crystal growth from solution will be given in Chapter 2.

In Chapter 3, the diastereoselective addition of allylzinc bromide to imines derived from (*R*)-phenylglycine amide ((*R*)-PGA) is described in detail. Chapter 3 deals with the reductive removal of the PGA chiral auxiliary, and in Chapter 4 the non-reductive removal is described. This general protocol proved to be widely applicable in the synthesis of a new family of substituted aromatic butylamines and butenylamines with high enantiomeric purity, which will find application in Dutch Resolution experiments. Furthermore, these chiral amines can be important building blocks in the synthesis of biologically active products and compounds of pharmaceutical interest.

Chapter 5 deals with the application of the family of arylbutylamines in the second generation Dutch Resolution of a number of racemic substrates. In these experiments, 1-phenylbutylamine was used as the parent resolving agent, and the substituted family members were used as additive.

Chapter 6 deals with the understanding of the role of an additive in the second generation Dutch Resolution of various racemic acids with 1-phenylethylamine as the parent resolving agent. 1-Phenylbutylamine was identified to be a potential nucleation inhibitor in the resolution process of mandelic acid on the basis of turbidity measurements. Subsequently, reasonably accessible family members of 1-phenylethylamine were examined to elucidate structure/activity relationships.

In the final chapter of this thesis, the epilogue, the leads and outlook in Dutch Resolution are discussed. The development and application of novel classes of polyfunctional resolving agents is described, a class that has not been used before in resolution experiments to our knowledge. Furthermore, some recommendations for future research on 'high-throughput screening' of (Dutch) resolution experiments are presented.

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Chapter 2
Crystal Growth from Solution

A large part of the success of Dutch Resolution lies most probably in the phenomenon called 'nucleation inhibition'. To understand this, it is important to gain insight into what occurs at the molecular level during the crystallization process of the diastereomeric salts in resolution experiments. The basic principles of crystal growth from solution will be briefly discussed in this chapter as a basis for understanding the role of nucleation inhibition in Dutch Resolution.

2.1 Introduction

The formation of crystalline material may occur from a melt, from a gaseous phase, from a supercritical fluid or from solution. Since in resolution experiments (either classical or Dutch Resolution) precipitation of diastereomeric salts takes place from solution, this chapter deals only with the latter. A general scheme of the preparation of enantio-enriched products by diastereomeric salt crystallization is given in Scheme 2.1.

substrate in solution → **generation of supersaturation** *driving force* → **nucleation** *birth of new crystals* → **crystal growth** *incorporation of crystal forming elements* → **enantioenriched final product**

Scheme 2.1 *General scheme of the preparation of enantio-enriched final products by diastereomeric salt crystallization.*

2.2 Supersaturation - The Driving Force[1,2]

A crystalline material is an ordered three-dimensional solid formed by regular repetition of the growth units. The most important requirement for crystallization is *supersaturation*, which is the driving force for nucleation to occur. Figure 2.1 shows a typical (super)solubility diagram.

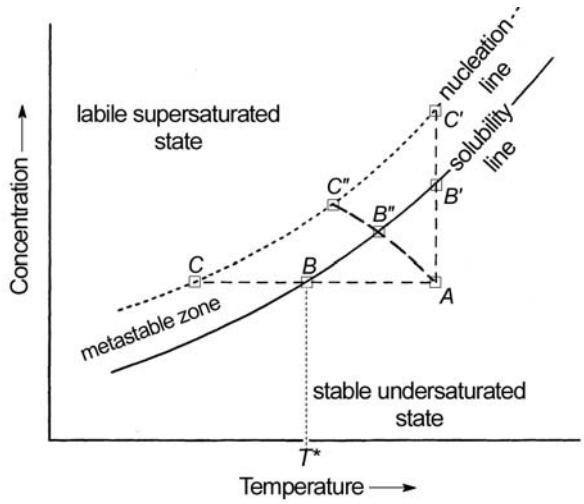


Figure 2.1 *Typical solubility/supersolubility plot.*

The diagram can be described in terms of three distinct zones:

[1] The stable zone of an undersaturated solution where no nucleation or crystal growth is possible. Existing crystals will simply dissolve,

[2] The supersaturated metastable zone where growth may occur but spontaneous nucleation does not, and

[3] The labile supersaturated zone of spontaneous and rapid nucleation.

The formation of a supersaturated solution is a prerequisite for crystallization to occur. Supersaturation can be reached by *e.g.*

- Cooling a saturated solution (corresponding to line *AC* in Figure 2.1),
- Concentrating a saturated solution by evaporation of solvent (corresponding to line *AC'*), or
- A combination of cooling and evaporation (corresponding to line *AC''*).

The generally used method in resolution experiments to induce precipitation of diastereomeric salts is (gradual) cooling. Cooling the solution with concentration c from the initial point A will lead to the point B on the solubility curve (Figure 2.1). At this point the solution becomes saturated. On further cooling the system becomes supersaturated but spontaneous nucleation to form crystals does not occur immediately in this region until a point C on the metastable boundary is reached. The following quantities are often used to define the state of supersaturation:[3]

Supercooling: $\Delta T = T^* - T$ (wherein T^* is the dissolution temperature, T is the actual temperature and $T^* > T$).

Concentration driving force: $\Delta c = c - c^*$ (wherein c is the actual concentration, c^* is the equilibrium dissolution concentration at a given temperature (at point B in Figure 2.1) and $c > c^*$).

Relative supersaturation: $\sigma = \frac{\Delta c}{c^*}$

Another parameter is the induction time τ_i. This corresponds to the time that passes until the first nucleus is formed in the supersaturated solution. The induction time decreases rapidly

with the increase of the degree of relative supersaturation; the higher the relative supersaturation, the sooner crystallization will start.

2.3 Primary Nucleation[4]

Primary nucleation is the first stage in the crystallization process. Simply defined, it represents the birth of a new crystal. Primary nucleation is believed to be initiated in a series of bimolecular collisions that forms an aggregate of a small number of molecules ('embryos') of the dissolved material.

$$A + A \rightleftharpoons A_2$$

$$A_2 + A \rightleftharpoons A_3$$

$$\vdots$$

$$A_n + A \rightleftharpoons A_{n+1}$$

Embryos below a critical cluster size (r_c), are unstable and may disintegrate, whereas embryos that exceed this critical cluster size will become stable nuclei and will grow (Figure 2.2).[5,6]

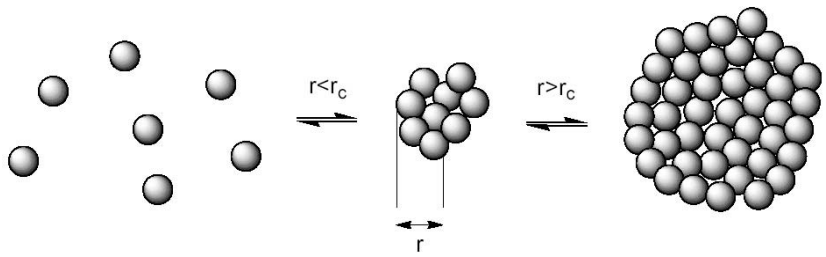


Figure 2.2 *The process of nucleation.*[7]

One should keep in mind that the size of these embryos is still beyond the limit of detection, even by dynamic light scattering. Consequently, an apparently optically clear supersaturated solution may nevertheless contain seeds. Therefore, prolonged heating is advisory to ensure total dissolution.

Classical nucleation theory states that the change in the Gibbs free energy (ΔG) required to form a nucleus of radius r is given by the equation:[8,9]

$$\Delta G(r) = \underbrace{-\left(\frac{4\,\pi r^3}{3\,\Omega}\right) k_B T \ln(1+\sigma)}_{\Delta G_V} + \underbrace{4\,\pi r^2 \gamma}_{\Delta G_S}$$

Wherein:

r : size of the cluster

Ω : specific volume of a growth unit

γ : solid-liquid interfacial energy

k_B : Boltzmann constant

σ : relative supersaturation (see section 2.2)

The first term in this equation is a bulk term (ΔG_V), which is negative and decreases as r^3, and the second term is a surface term (ΔG_S), which is positive and increases as r^2 (Figure 2.3).

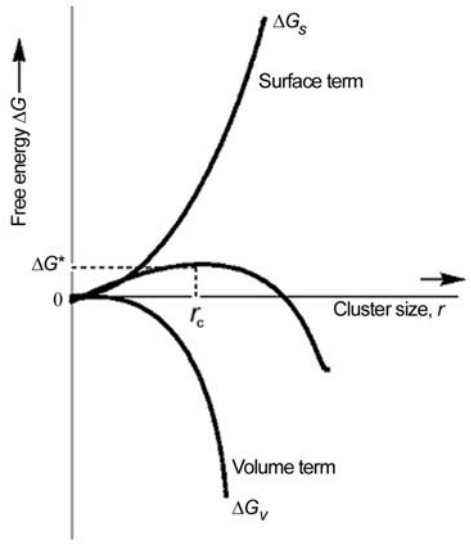


Figure 2.3 *Gibbs free energy change of nucleation as a function of the cluster size.*[7]

As can be seen in Figure 2.3, as result of the surface and volume term the ΔG passes through a maximum, denoted as ΔG^*. Taking the derivative with respect to r and setting this equal to zero allows calculation of r_c. This value of r_c is called the *critical cluster size*.

$$r_c = \frac{2\,\Omega\,\gamma}{k_B \ln(1+\sigma)}$$

Inserting this value of r_c into the original equation yields the activation energy necessary to form a nucleus of the critical size (ΔG^*):

$$\Delta G^* = \frac{16\,\pi\,\Omega^2\,\gamma^3}{3\,[k_B\,T\,\ln(1+\sigma)]^2}$$

Figure 2.4 shows the dependence of ΔG^* on the relative supersaturation σ. As the supersaturation increases, both the barrier for the critical activation energy and the value of the critical size decrease. Eventually, as the degree of supersaturation increases, the activation energy becomes so low that spontaneous and rapid nucleation occurs.

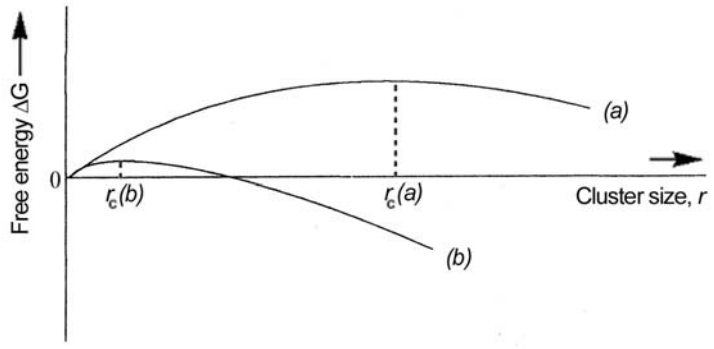


Figure 2.4 *Gibbs free energy change of nucleation as a function of the cluster size at low supersaturation (a) and at high supersaturation (b).*[10]

The rate of nuclei formation (J), defined as the number of clusters that grow further than the critical size and so become crystals, is given by the equation

$$J = J_0 \exp\left(\frac{-\Delta G^*}{k_B\ T}\right)$$

Since the activation energy is a decreasing function of the supersaturation, the rate of nucleation increases with the increase of the supersaturation. A large rate of nucleation is accompanied by a small τ_i value.

2.4 Secondary Nucleation – Entrainment

While in primary nucleation crystals can grow but cannot spontaneously nucleate in the metastable zone, secondary nucleation is due to the presence of existing crystals. By deliberate addition ('seeding') of crystals of one of the individual enantiomers in the metastable zone, one can crystallize one enantiomer of a racemate preferentially. This process is called *resolution by entrainment* or *preferential crystallization* and is widely used in industrial processes.[11,12] Resolution by entrainment was first observed by Desiré Gernez, who was a student of Pasteur. He found that on seeding a supersaturated solution of racemic sodium ammonium tartrate with one of the enantiopure enantiomers, the stereoselective nucleation and crystal growth of crystals with the same stereochemistry as the seed is triggered.[13] The prime requirement, however, for resolution by entrainment is that the racemate of interest crystallizes as a *conglomerate*. A conglomerate is a mixture of crystals of individual enantiomers that can, in principle, be separated mechanically. It is estimated that only 5–10 % of pairs of enantiomers crystallize as a conglomerate.[11b]

Other possibilities to crystallize one enantiomer preferentially are the use of nucleation inhibitors (as will be described in section 2.8) or the use of chiral solvents.[14]

2.5 Crystal Growth[15,16]

Once an ordered structure is formed by nucleation, the growth units (atoms, ions or molecules) can diffuse from the surrounding supersaturated solution to the surface of the nuclei and incorporate into the lattice resulting in crystal growth.[17]

A graphical representation of the crystal growth mechanism is shown in Figure 2.5. This schematic simple cubic crystal used for illustration is referred to as a Kossel crystal.[18] As indicated, adsorption of the crystal forming elements (depicted as a cube) on the surface structure of a growing crystal may occur at three possible sites:

[1] Ledge sites (incorporation at a flat surface (terrace) having only one site of intermolecular interaction available),

[2] Step sites (incorporation at a surface having two sites of intermolecular interactions available), or

[3] Kink sites (three possible sites of intermolecular interactions).

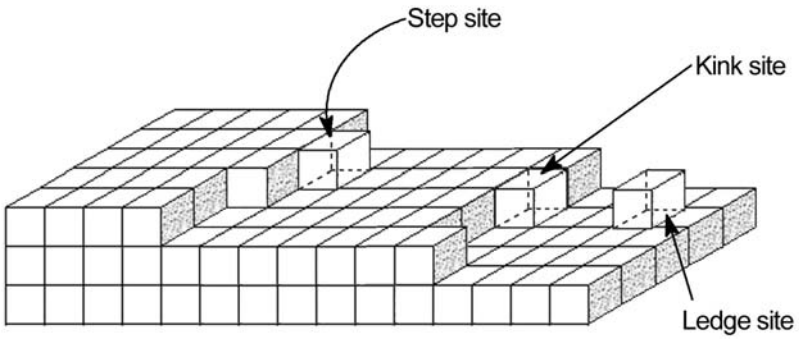


Figure 2.5 *Incorporation of crystal forming elements on the surface of a growing crystal.*

Because crystal forming elements with the highest coordination number are bound most strongly to the surface, incorporation at a kink site will be the most energetically favorable. Furthermore, since incorporation at a kink site will provide a new kink site, the kink site is thus a 'repeatable step' in the formation of the crystal.

Crystal growth can follow two possible mechanisms: spiral growth at screw-dislocations or two-dimensional nucleation.

2.5.1 Two-dimensional Growth[19,20]

In two-dimensional growth, before grow can occur, a monolayer island nucleus, usually called a 'two-dimensional nucleus', must come into existence on an existing layer (Figure 2.6*a*). This island becomes the source of new steps and kink sites at which additional units can join the surface. Subsequent crystal forming elements will tend to incorporate at sites where attractive forces are greatest, *i.e.* they will migrate towards the energetically favorable kink sites (Figure 2.6*b*). The step-growth will advance until the whole plane is completed (Figure 2.6*c*) and a new two-dimensional nucleus has to be generated before growth can advance. This two-dimensional growth mechanism is also known as the 'birth and spread' model; after nucleation ('birth') of a monolayer island it can grow ('spread') laterally across the surface. Two-dimensional growth is only expected to occur at relatively higher supersaturation since it is difficult to generate a nucleus on an already existing flat crystal surface.

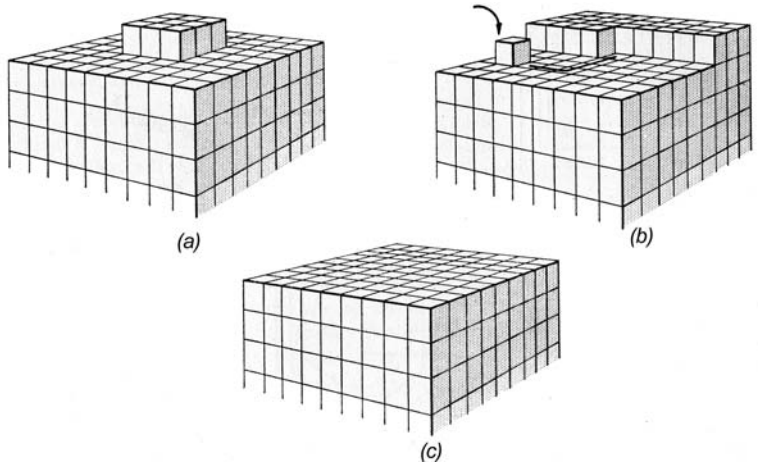


Figure 2.6a-c *Two-dimensional nucleation.*[20]

2.5.2 Screw Dislocations

It is necessary to have a model that describes growth at low supersaturations, since two-dimensional growth only occurs at high supersaturations. At low supersaturation, growth occurs along screw dislocations (Burton-Cabrera-Frank (BCF) model).[21] This model (Figure 2.7) is based on a defect in the structure of the crystal lattice formed by stress inside the crystal lattice, which produces spiraling mounds.[22] These steps of monomolecular height provide energetically favorable positions for further deposition, comparable to kink sites in the two-dimensional growth model. From Figure 2.7 it can be seen that these screw dislocations in the crystal are a continuous source of new steps and that this screw mechanism provides a way for steps to grow uninterrupted. Therefore a lower degree of supersaturation is required than for the two-dimensional nucleation.

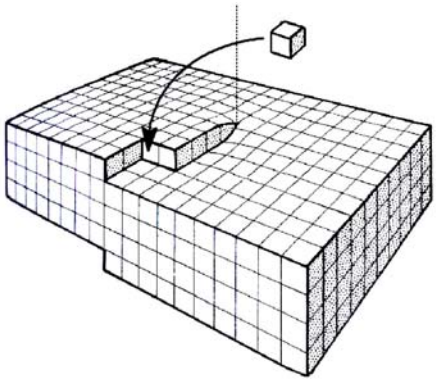


Figure 2.7 *Spiral growth from a screw.*

2.6 Crystal Habit

The crystal habit, or morphology, is the external shape of a crystal and is governed by the different rates of growth of the various faces that bound the crystal. The growth of certain faces may be preferred over others and the shape of the growing crystals will be determined by the presence or absence of dominant growth directions (Figure 2.8).[1]

Crystals that grow nearly uniformly in all three dimensions will become cubic. If the crystals grow mainly along one plane, the habit will become tabular or plate-like. Finally, if the crystal grows mainly in one direction it will assume a needle-like form. In general, the slowest growing faces are those that determine the habit.

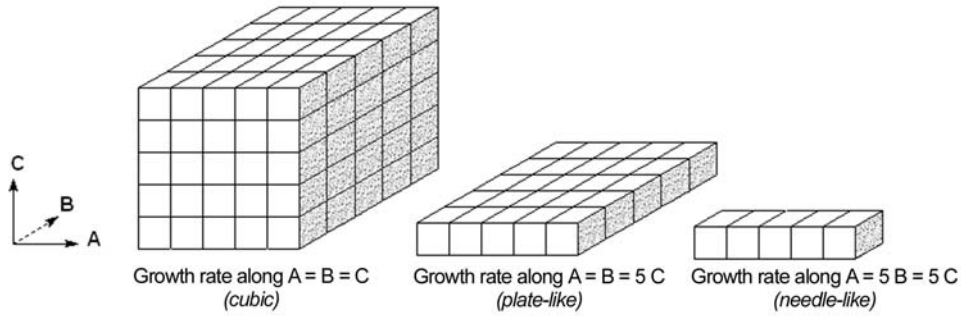


Figure 2.8 *Effect of growth rate of different faces on the resulting crystal habits.*

Since many chemical processes rely on the isolation of the final product by crystallization, the control of crystal size and their size distribution is important since this will determine the ease and efficiency with which the crystals can be separated by filtration or centrifugation. Crystals that are needle-like in shape tend to pack as impervious layers and cause problems in filtration, whereas crystals with cubic habits result in layers that filter well.[19]

The habit of a crystal can vary depending on the environment in which it is grown. A number of factors can affect the habit of a crystal. These include solvent, pH, impurities, supersaturation, and temperature.[23]

2.7 Habit Modifiers

Habit modifiers, either present as impurities or added deliberately, have a profound effect on growth rate of one or more faces, even at very low concentrations. These impurities can be any substance other than the material being crystallized. Therefore even the solvent from which the crystals are grown can be considered to be an impurity. If impurities are

deliberately added to produce a desired morphological change, they are referred to as 'additives'.

By adsorbing on specific faces, impurities or additives can retard and eventually even stop growth. In Figure 2.9 the step mechanism of growth of two layers at a surface is depicted schematically. In this cross section, layer **I** grows on top of the lower positioned layer **II**, and layer **II** grows in the same direction on the lower positioned layer **III**. From the surrounding supersaturated solution the crystal forming elements adsorb on the surface and the layers grow in the indicated direction and the rate of growth depends on the relative rates of separation and incorporation.

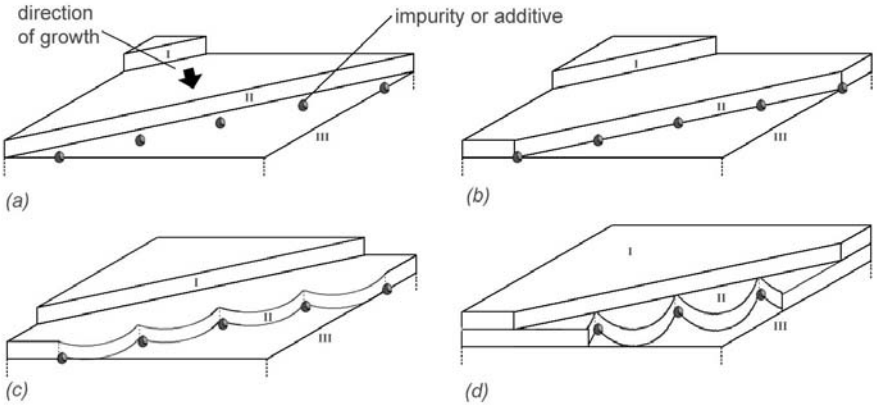


Figure 2.9a-d *Effect of adsorption of additives or impurities on layer growth.*

When impurities or additives become strongly adsorbed on a growing surface (*e.g.* layer **III**, Figure 2.9*a*), the growth of layer **II** adjacent to such sites is retarded and eventually can stop completely (Figure 2.9*b–d*). Subsequently, the growth of layer **I** will be inhibited (Figure 2.9*d*). Because the "concentration" of active growth sites is so low, very low concentrations of impurities or additives can retard or stop further growth.[19] Once a certain level of supersaturation is reached, the additive is either released or the additive will be overgrown and becomes incorporated in the crystal.

Urea and hexacyanoferrate(II) are known habit modifiers in the crystallization of sodium chloride (Figure 2.10).[1,15c] In pure solution (without a modifier), sodium chloride crystallizes with a cubic habit. In the presence of only 1 ppm urea, crystals of sodium chloride are obtained with an octahedral habit. In the presence of 1 ppm hexacyanoferrate(II) the habit changes to a dendritic habit.

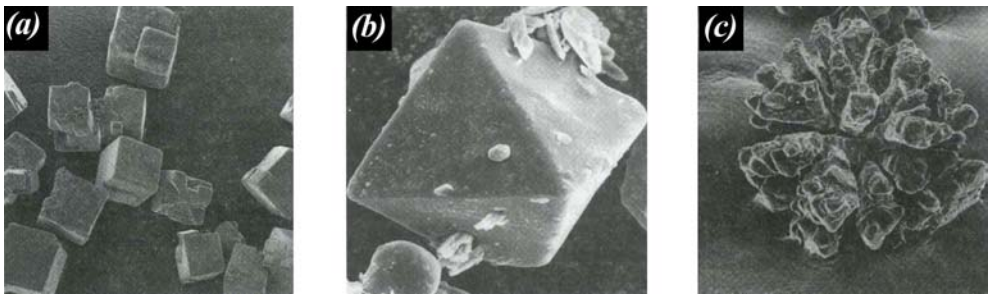


Figure 2.10a-c *Crystallization of sodium chloride in (a) the absence of a habit modifier, (b) the presence of 1 ppm urea, and (c) the presence of 1 ppm hexacyanoferrate(II).*[24]

Special cases of additives are 'tailor-made additives'.[25] These man-made additives closely resemble the chemical structure of the crystallizing solute and are designed to adsorb or incorporate selectively into the lattice on specific crystal faces to produce a desired morphological change.[26]

From Figure 2.11 it can be seen how selective adsorption of tailor-made additives on the fast growing faces of a needle-like growing crystal gives rise to a more isomorphic shape.

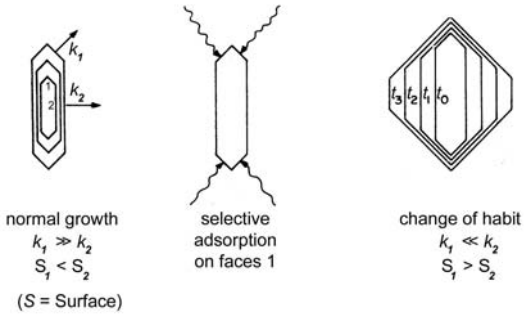


Figure 2.11 *Specific adsorption on fast growing faces of a needle-like crystal and the corresponding morphology change.*[4]

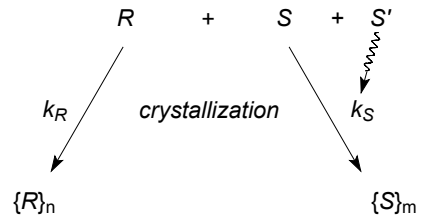
The use of tailor-made additives in the resolution of conglomerates was thoroughly studied by Lahav and co-workers.[26b,27] The addition of enantiopure tailor-made additives induced a stereoselective and substantial change in crystal morphology of the enantiomers of the conglomerate with the same absolute configuration, leaving the other enantiomer unaffected.[27a]

2.8 Nucleation Inhibitors

If the tailor-made additive becomes so efficient at blocking the growth sites that the initial nucleation of the crystals is blocked, it becomes a 'tailor-made inhibitor' (or 'nucleation inhibitor') rather than a modifier. Due to the nucleation-inhibiting effect of the additive, the metastable zone width of one of the enantiomers is enlarged. Because of the mirror-image relationship of the crystal lattices in conglomerates, to affect only one of the enantiomers (and not the other), the inhibitor itself should be chiral.

> **Inhibitor** [chem] A substance which is capable of stopping or retarding a chemical reaction; to be technical useful, it must be effective in low concentration.
>
> Source: *McGraw-Hill Dictionary of Scientific & Technical Terms,* Fifth Edition (*New York).*

Nowadays, the application of tailor-made additives to control crystallization processes is a subject of much interest. The addition of a structurally similar nucleation inhibitor (in amounts of 1–2 %) in the resolution of conglomerates is sufficient to inhibit the nucleation of the same enantiomorph. Consequently, the enantiomorph of opposite chirality precipitates in excess.[28] This process is illustrated in Scheme 2.2, where *S'* is the additive, both similar in stereochemistry and chemical structure of the unwanted enantiomer *S*. In the absence of *S'*, k_R is equal to k_S. In the presence of *S'*, k_R and k_S become dissimilar ($k_R >> k_S$). The effectiveness of this principle has been demonstrated for many systems.[29]



Scheme 2.2 *Use of nucleation inhibitors in the resolution of conglomerates.*[28]

To our best knowledge, the work described by Nieuwenhuijzen *et al.* is the first example of extension of this principle to the resolution of diastereomeric crystalline salts.[30] In this second generation Dutch Resolution protocol, described in Chapter 1.5.2 of this thesis, structurally related family members interact with the unwanted diastereomeric salt by delayed crystallization in a manner similar to the role played by the tailor-made inhibitors discussed above. One must keep in mind that, since in resolutions by diastereomeric salt formation the crystal structures of both salts do not have a mirror-image relationship, the additive does not necessary have to be chiral.

2.9 References

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Chapter 3

Diastereoselective Allylation of Imines derived from (*R*)-Phenylglycine Amide

The synthesis of enantio-enriched 1-aryl-1-butylamines via a highly diastereoselective addition of allylzinc bromide to imines derived from (R)-phenylglycine amide is described. A three-step procedure is applied, which involves: (a) formation of the chiral imines; (b) asymmetric addition of the allylzinc reagent; (c) removal of the chiral auxiliary under reductive conditions. This overall protocol leads to a broad range of 1-aryl-1-butylamines with high enantiomeric purity, which can be used in Dutch Resolution experiments. The scope and limitations of the reductive removal step will also be discussed.

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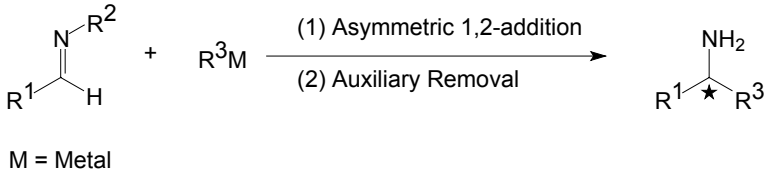
3.1 Introduction

Enantiomerically pure amines with a stereogenic centre at the α-position are valuable synthons in the synthesis of biologically active natural products and compounds of pharmaceutical interest.[1] One of the strategies used to obtain enantiomerically pure amines is an asymmetric 1,2-addition of nucleophiles to the electrophilic C=N imino group of chiral aldimines[2] or hydrazones[3] (Scheme 3.1). Other methods include *e.g.* catalytic asymmetric addition of dialkylzinc to imines,[4] diastereoselective reduction of chiral imines,[5] asymmetric reduction of prochiral imines and enamides[6] and oximes[7] or use of a transaminase.[8] The most frequently employed methodology for the synthesis of homoallylamines is the allylation of imines or hydrazones by allyl Si, Sn, Sm, Li, Mg, Zn, Ce, Cr, B, Ba or Cr reagents.[3c, 9,10]



Scheme 3.1 *Synthesis of enantiomerically enriched primary amines by asymmetric 1,2-addition.*

Enantiopure imines can be generated, in most cases fairly easily, by condensation of an enantiopure amine R^2-NH_2 used as a (readily available) chiral auxiliary, with the corresponding carbonyl compound. High asymmetric induction during the addition has been reported by using imines derived from chiral auxiliaries such as α-arylethylamines,[11] β-amino alcohols, β-alkoxy amines, and β-amino acid esters.[12] A common feature of the latter three auxiliaries is the presence of a second heteroatom, which is capable of rigidifying the transition state of the 1,2-addition through chelation.[11] This effect is also referred to as "chelation control".[13] Possible drawbacks in the use of chiral auxiliaries are the availability, in some cases, of only one enantiomer, high costs, low regioselectivity in the cleavage of the auxiliary, immolative removal and/or the need of removal of these auxiliaries by procedures unsuitable for large-scale preparations (*i.e.* oxidation with $Pb(OAc)_4$ [14] or treatment with $HIO_4/MeNH_2$).[10c,11,12b] Often the obtained enantiomeric excesses (*ee*'s) are not satisfactory.[5c,6,7,15]

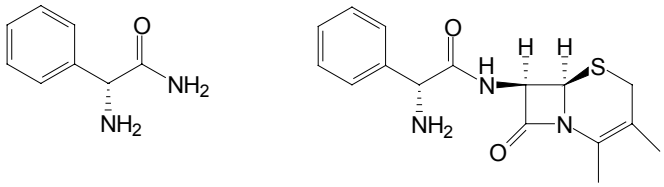
In the next two chapters the preparation of easily accessible substituted 1-aryl-1-butylamines and 1-aryl-3-butenylamines is described, which we intend to use as new families of resolving agents in "Dutch Resolution experiments".[16] A metal-mediated Cope reaction (Figure 3.1) is a key element of the synthesis. There is extensive precedent for such reactions.[9b,9g,17a]

M = Si, Sn, Sm, Li, Mg
Zn, Ce, Cr, B, Cr

X = O, N, *etc*

Figure 3.1 *Metal-mediated (aza-)Cope reaction.*

In preliminary publications, (*R*)-phenylglycine amide, (*R*)-PGA (**3.1**), was shown to be a highly efficient chiral auxiliary for this process.[17a,17c] Enantiomerically pure (*R*)-PGA (**3.1**) is a key intermediate in the industrial (enzymatic) route for the preparation of cephalexin, a semi-synthetic antibiotic, in which (*R*)-PGA is incorporated.[18]



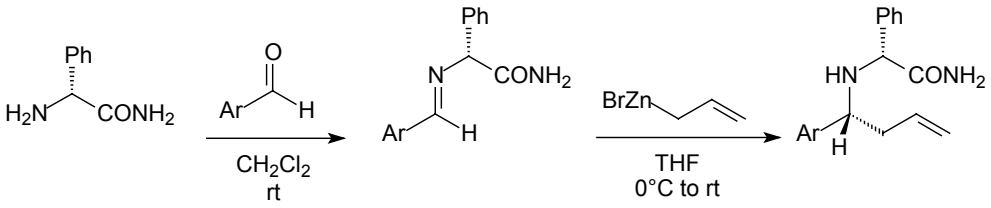
(*R*)-PGA, **3.1** Cephalexin

In this chapter we expand upon the scope of the metal-mediated aza-Cope reaction. The imines derived from (*R*)-PGA, are capable of forming rigid chelated intermediates, and have been subjected to addition of allylzinc reagents. Both reductive and non-reductive methods for the removal of the chiral auxiliary have been used to obtain the desired substituted enantiomerically pure primary amines. In this chapter, the reductive removal of the (*R*)-PGA chiral auxiliary will be discussed. Finally, the selectivity of cleavage of the chiral auxiliary in the reductive removal has been investigated.

3.2 Formation of (*R*)-PGA Aldimines

Aldimines (*R*)-**3.2**–**3.29** are easily obtained in excellent yields and > 99 % *ee* [19] by stirring a mixture of (*R*)-PGA (**3.1**) and the corresponding substituted benzaldehyde (ArCHO) in CH_2Cl_2 overnight at room temperature (Table 3.1).[17] In practically all cases no catalyst is required, although the formation of aldimine (*R*)-**3.27** required elevated temperatures and acid catalysis. In all cases, after removal of the water and the CH_2Cl_2, chemically pure and stereochemically homogeneous products were obtained. This conclusion is based on the fact that clean singlets for both the proton adjacent to the carboxamide group as well as the imine proton are observed in the ^{1}H-NMR spectra. Imines **3.2**–**3.29** are crystalline and have sharp melting points. On the basis of thermodynamic considerations the products should all have the *E*-configuration. This was confirmed by COSY- and NOESY-2D NMR spectroscopy. After work-up, the CH_2Cl_2 can be easily re-used without further purification.

Table 3.1 *Formation of (R)-PGA imines **3.2**–**3.29** by condensation with substituted benzaldehydes and the formation of (R,R)-PGA homoallylamines **3.33**–**3.60** by addition of allylzinc bromide.*



(*R*)-PGA, **3.1** (*R*)-**3.2**-**3.29** (*R,R*)-**3.33**-**3.60**

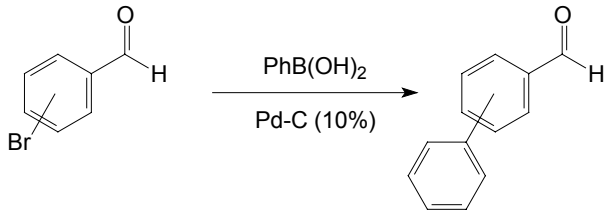
Entry	Imine	Ar	Yield (%)[a]	Allylamine	Yield (%)[a]	*dr* (*R,R*):(*R,S*)[b]
1	**3.2**	C_6H_5	99	**3.33**	>99	>99:1
2	**3.3**	*o*-Me C_6H_4	>99	**3.34**	93	99:1
3	**3.4**	*m*-Me C_6H_4	97	**3.35**	>99	>99:1
4	**3.5**	*p*-Me C_6H_4	>99	**3.36**	97	>99:1
5	**3.6**	*o*-OMe C_6H_4	93	**3.37**	98	>99:1
6	**3.7**	*m*-OMe C_6H_4	81	**3.38**	99	>99:1
7	**3.8**	*p*-OMe C_6H_4	98	**3.39**	99	>99:1
8	**3.9**	*o*-F C_6H_4	97	**3.40**	>99	98:2

Entry	Imine	Ar	Yield (%)[a]	Allylamine	Yield (%)[a]	*dr* (*R*,*R*):(*R*,*S*)[b]
9	**3.10**	*m*-F C_6H_4	96	**3.41**	97	98:2
10	**3.11**	*p*-F C_6H_4	95	**3.42**	94	99:1
11	**3.12**	*o*-Cl C_6H_4	97	**3.43**	98	97:3
12	**3.13**	*m*-Cl C_6H_4	98	**3.44**	83	98:2
13	**3.14**	*p*-Cl C_6H_4	95	**3.45**	98	>99:1
14	**3.15**	*o*-Br C_6H_4	99	**3.46**	98	>99:1
15	**3.16**	*m*-Br C_6H_4	98	**3.47**	99	>99:1
16	**3.17**	*p*-Br C_6H_4	99	**3.48**	95	>99:1
17	**3.18**	*o*-Ph C_6H_4	85	**3.49**	89	>99:1
18	**3.19**	*m*-Ph C_6H_4	89	**3.50**	85	>99:1
19	**3.20**	*p*-Ph C_6H_4	95	**3.51**	99	>99:1
20	**3.21**	*o*-NO_2 C_6H_4	97	**3.52**	>99	>99:1
21	**3.22**	*m*- NO_2 C_6H_4	98	**3.53**	96	>99:1
22	**3.23**	*p*- NO_2 C_6H_4	92	**3.54**	93	99:1
23	**3.24**	*o*-OH C_6H_4	97	**3.55**	95	>99:1
24	**3.25**	*m*-OH C_6H_4	98	**3.56**	97	>99:1
25	**3.26**	*p*-OH C_6H_4	92	**3.57**	95	99:1
26	**3.27**[c]	3-Piperonyl	85	**3.58**	81	>99:1
27	**3.28**	1-Naphthyl	83	**3.59**	95	>99:1
28	**3.29**	2-Naphthyl	91	**3.60**	73	>99:1

[a] Isolated yield. [b] Diastereomeric ratios were determined with ^{1}H-NMR spectroscopy. [c] In $CHCl_3$ with catalytic *p*-$TolSO_3H$ for 2h at reflux.

The phenyl-substituted benzaldehydes for the formation of imines **3.18**–**3.20** were prepared from the corresponding bromobenzaldehydes by a Suzuki coupling using 10 % palladium on carbon as a heterogeneous catalyst (Table 3.2).

Table 3.2 *Preparation of phenyl-substituted benzaldehydes **3.30**–**3.32** via a Pd-C catalyzed Suzuki coupling. Reagents and conditions: i-propanol/H_2O/Na_2CO_3, Pd-C (10%), $PhB(OH)_2$, 65 °C.*[20]



3.30-3.32

Entry	Ar	Arylaldehyde	Yield (%)
1	*o*-Br C_6H_4	**3.30**	93
2	*m*-Br C_6H_4	**3.31**	94
3	*p*-Br C_6H_4	**3.32**	95

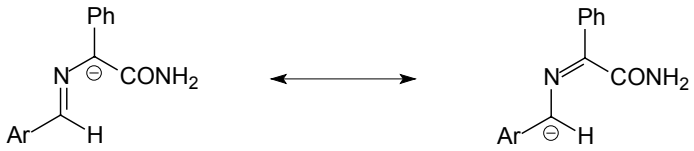
This palladium source is relatively inexpensive and can easily be removed. The palladium on carbon catalyzed Suzuki reaction has been used recently for the preparation of a range of resolving agents based on 4-arylmandelic acid derivatives.[21] Attempts to perform a Suzuki coupling reaction in a later stage of the synthetic route failed.

3.3 Diastereoselective Allylation of (*R*)-PGA Aldimines

The addition of aldimines (*R*)-**3.2**–**3.29** to preformed allylzinc bromide (1.5 equiv.) in THF at 0 °C afforded the (*R,R*)-PGA allylamines **3.33**–**3.60** in yields up to 99 % and *dr*'s of at least 97:3 (Table 3.1). In all cases, the *dr* could be increased to more than 99:1 by recrystallization from acetone/hexane (1:20). The configurations of the stereogenic centers were determined by X-ray analysis and will be discussed later in this paragraph.

Allylzinc bromide proved to be the organometallic reagent of choice since it is easily prepared and compatible with most organic functional groups.[22] Note that the phenylglycine amide chiral auxiliary in imines **3.2**–**3.29** contains a chiral center that could

potentially racemize under basic conditions. Removal of the proton at the α-position of the phenylglycine moiety would give a 2-aza allyl anion (Scheme 3.2).[23] The resulting carbanion could be stabilized by both the adjacent carbon-nitrogen double bond as well as the carboxamide group.



Scheme 3.2 *2-Aza allyl anion resonance structures.*

Despite these potential problems, it has been demonstrated previously by chiral HPLC that the addition reaction proceeds without any racemization of the chiral auxiliary for the cases **3.33** and **3.58**.[17a] However, although this has not been explicitly checked, the *ee*'s of the end products indicate that this is also the case for the other addition products **3.34**–**3.60** (*vide supra*).

The addition reaction has also been performed under Barbier-type conditions with imines **3.2**–**3.11**, **3.18**–**3.20** and **3.28**–**3.29** giving similar results. "Barbier conditions" are referred to as reactions wherein the organometallic reagent is formed *in situ*. In this procedure the imines are stirred with zinc and allyl bromide in THF at 0 °C and the reaction mixture is allowed to warm to room temperature. This procedure in our experience is considerably easier from an experimental point of view.

The compatibility of allylzinc bromide with relatively acidic functionalities such as an amide or hydroxyl group is remarkable. In view of the approximate relative *pKa* of 17 for amides,[24] the basic allylzinc reagent could well be protonated by the amide group. The lack of reaction with an even more acidic functionality such as a phenolic hydroxyl group (*pKa* 8–11) is even more striking (entries 23–25). The addition of 1.5 equiv. of allylzinc bromide to *(R)*-**3.24**–**3.26** furnished homoallylamines *(R,R)*-**3.55**–**3.57** as the only products in up to 97 % isolated yields.

For determination of the diastereoselectivity with ^{1}H–NMR, analogous reactions were performed with magnesium turnings.[25] This process furnishes the adducts with lower *dr* values. The ratio of (*R,R*) and (*R,S*) can be determined from the integrals of the vinylic proton (ν), which is typically in the region of 5.3–5.9 ppm in the ^{1}H-NMR spectra, as

shown below in the case of PGA allylamine **3.39** obtained by reaction with the more reactive allylic Grignard reagent (Figure 3.2).

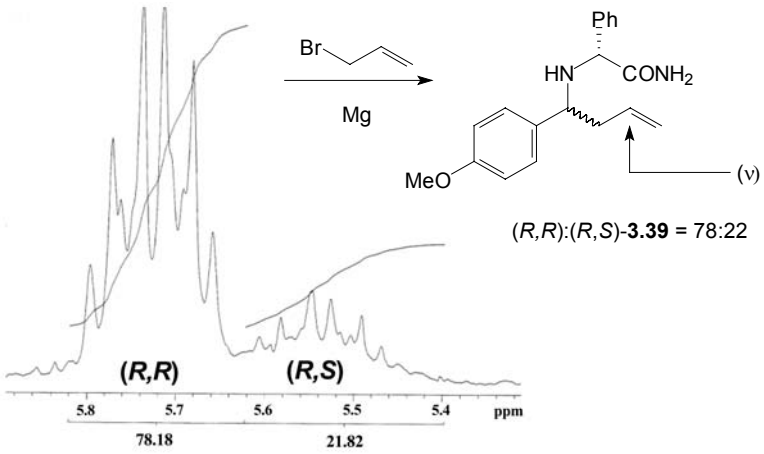


Figure 3.2 *Analogous reactions with more basic allylmagnesium bromide lead to lower dr values.*

The high diastereoselectivity of the Zn-mediated allylation of the (*R*)-PGA imines can be rationalized by chelation control, as shown in Figure 3.3.[9] The two heteroatoms of the amide-imine moiety chelate the zinc atom of the allylzinc reagent to form a five-membered ring.[11,13] Simultaneously, a six-membered chair-like transition state can be formed with the allylic system and the C=N double bond of the imine. The *re*-face 1,2-addition proceeds in a concerted fashion via an allylic aza-Cope-like rearrangement.

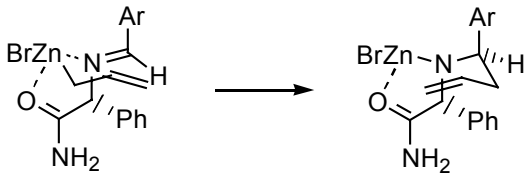
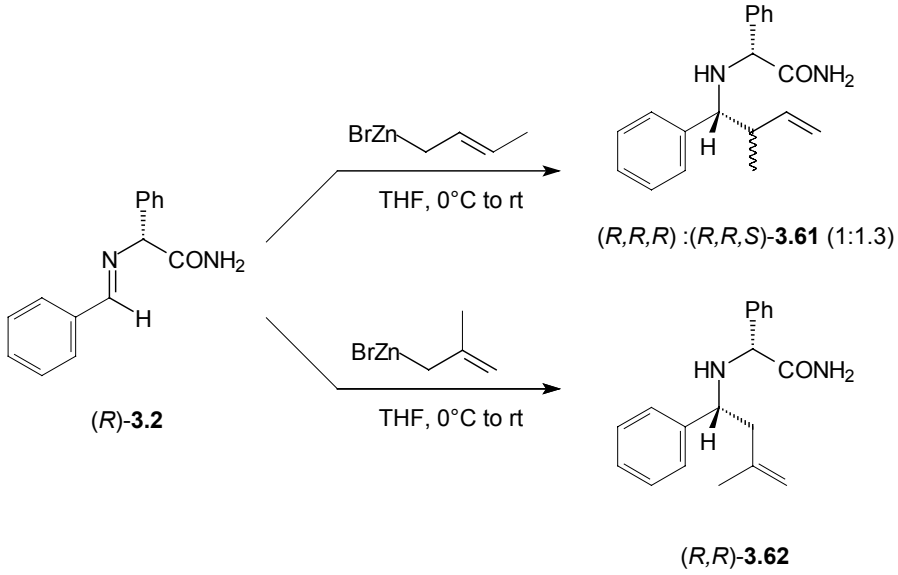


Figure 3.3 *Proposed chelation controlled addition of allylzinc bromide to (R)-PGA imines.*

The allylic rearrangement was confirmed by addition of crotylzinc bromide[26] to benzaldimine (*R*)-**3.2** (Scheme 3.3). Product **3.61** was isolated in 98 % yield (*dr* > 99:1) as a mixture of two isomers in a ratio of 1:1.3. As a demonstration of this scope, the addition of methallylzinc bromide to **3.2** furnished (*R*,*R*)-**3.62** in 98 % isolated yield (*dr* > 99:1).[17a]



Scheme 3.3 *The addition of crotylzinc bromide and methallylzinc bromide to imine **3.2**.*

In accord with the model proposed in Figure 3.3, the absolute configuration of the adducts **3.33**–**3.60** should be *(R,R).* This was unambiguously established by X-ray crystallographic analysis of **3.57** (Figure 3.4).[17a,27] The absolute configuration of adducts **3.33**–**3.60** is assigned by analogy.

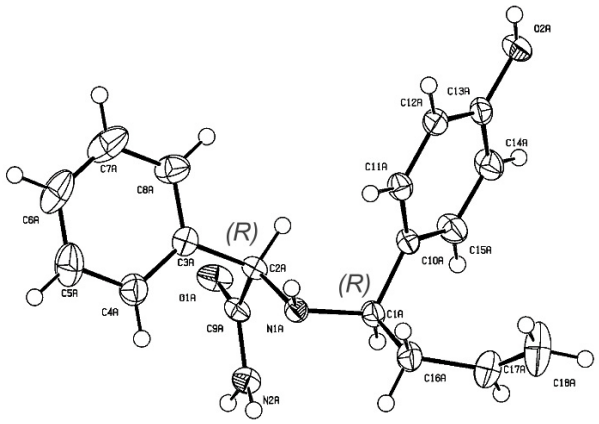
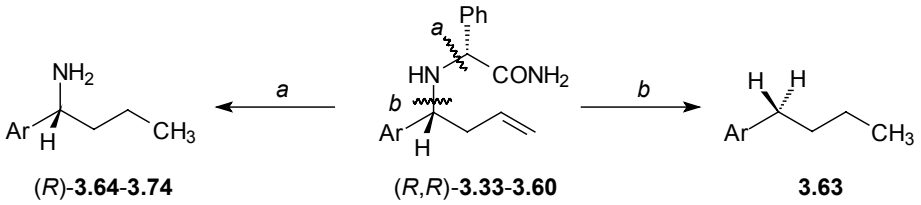


Figure 3.4 *X-ray structure of (R,R)-**3.57**.*

3.4 Reductive Removal of the Chiral Auxiliary

The chiral auxiliary can easily be removed by selective catalytic debenzylation using H_2 and 10 % palladium on carbon in *i*-propanol and aqueous acetic acid.[28,29] The amines were hydrogenolysed in an acidic medium to eliminate the poisoning effect of the basic nitrogen on the catalyst. However, since PGA allylamines **3.33**–**3.60** are 'di-*N*-benzylic', reductive removal of the auxiliary by catalytic hydrogenation may proceed via route *a* or route *b* (Scheme 3.4). In addition, this reductive removal of the chiral auxiliary leads to reduction of the allylic double bond.

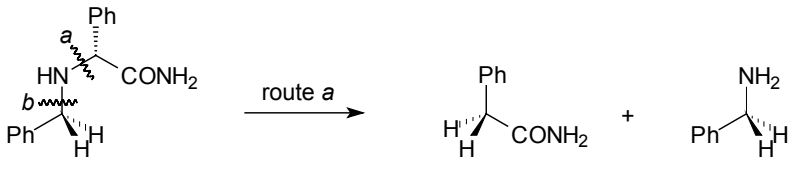


(*R*)-**3.64**-**3.74** (*R*,*R*)-**3.33**-**3.60** **3.63**

Scheme 3.4 *Selectivity of cleavage in the catalytic hydrogenation process. Reagents and conditions: i-propanol/H_2O/AcOH, H_2, Pd-C (10 %).*

Hydrogenolytic cleavage via route *b* leads to the undesired substituted 1-butylbenzene **3.63**, whereas cleavage via route *a* provides the desired saturated 1-arylbutylamines (*R*)-**3.64**–**3.74**.

There is not much literature precedent to allow prediction whether path *a* or path *b* will dominate, although steric and electronic effects are expected to influence the outcome of the hydrogenolysis in a predictable fashion. With this in mind we began a systematic investigation. Initially 2-(benzylamino)-2-phenylacetamide **3.75** [30] was examined as a model compound (Scheme 3.5) and we were very much encouraged to observe only benzylamine and phenylacetamide **3.76** (route *a*). The formation of toluene and (*R*)-PGA **3.1** were not observed (route *b*).



3.75 **3.76**

Scheme 3.5 *Regioselectivity in the debenzylation process of **3.75**. Reagents and conditions: Et_2O, H_2, Pd-C (10%).*

The electron-withdrawing carboxamide group, by means of inductive interactions, withdraws some electron density from the sigma bond involved in path *a*. One could therefore well expect this sigma bond to be a better hydrogen acceptor.

The selectivities (*a*:*b*) for products **3.64**–**3.74** were determined by ^{1}H-NMR spectroscopy.[17c] Analysis of ^{1}H-NMR spectra of the reaction mixtures revealed that cleavage according to route *a* gave rise to a characteristic triplet of the benzylic CH-group between δ = 3.9–4.2 ppm, and competitive cleavage according to route *b* gave rise to a triplet of the benzylic CH_2-group at approx. δ = 2.5–2.8 ppm. By comparing the ratio of the integrals for both signals, the selectivity for each case could be determined (Table 3.3). For instance, in the case of the unsubstituted PGA allylamine **3.33** the selectivity of the cleavage process is 91:9 in favour of path *a* (Figure 3.5).

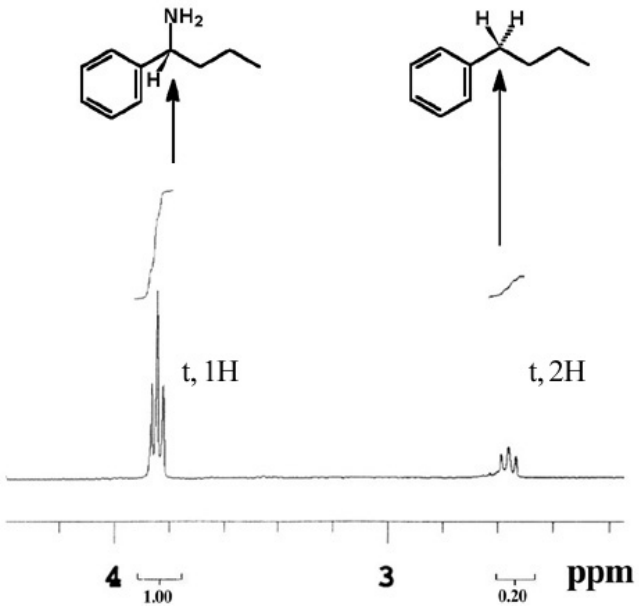


Figure 3.5 *Selectivity of cleavage of homoallylamine **3.33** after hydrogenation.*

Table 3.3 *Regioselective cleavage of the chiral auxiliary and generation of primary 1-aryl-1-butylamines* ***3.64–3.74*** *and* ***3.82*** *by catalytic hydrogenation.*

Entry	Allylamine	Ar	Butylamine	Yield [%] [a]	Selectivity *a*:*b* [b]
1	**3.33**	C_6H_5	**3.64**	70	91:9
2	**3.34**	*o*-Me C_6H_4	**3.65**	95	>99:1
3	**3.35**	*m*-Me C_6H_4	**3.66**	92	>99:1
4	**3.36**	*p*-Me C_6H_4	**3.67**	91	>99:1
5	**3.37**	*o*-OMe C_6H_4	**3.68**	91	>99:1
6	**3.38**	*m*-OMe C_6H_4	**3.69**	89	98:2
7	**3.39**	*p*-OMe C_6H_4	**3.70**	89	97:3
8	**3.40**	*o*-F C_6H_4	**3.71**	88	98:2
9	**3.41**	*m*-F C_6H_4	**3.72**	58	>99:1
10	**3.42**	*p*-F C_6H_4	**3.73**	79	>99:1
11	**3.49**	*o*-Ph C_6H_4	**3.74**	87	97:3
12	**3.50**	*m*-Ph C_6H_4	**3.77**	*nd*	>1:99 [c]
13	**3.51**	*p*-Ph C_6H_4	**3.78**	*nd*	>1:99 [c]
15	**3.55**	*o*-OH C_6H_4	**3.79**	*nd*	>1:99 [c]
16	**3.56**	*m*-OH C_6H_4	**3.80**	*nd*	>1:99 [c]
17	**3.57**	*p*-OH C_6H_4	**3.81**	*nd*	>1:99 [c]
18	**3.58**	*3*-Piperonyl	**3.82**	80	>99:1

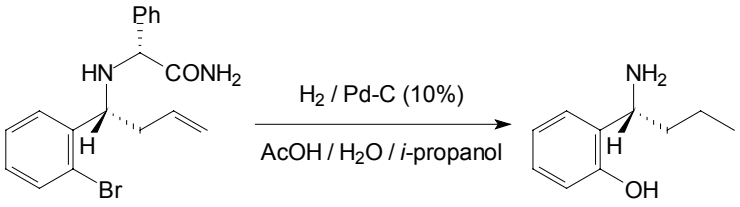
[a] Isolated yield. [b] Regioselectivity values were determined with ^{1}H-NMR spectroscopy. [c] Confirmed by mass analysis, ^{1}H- and ^{13}C-NMR. *nd*: Not determined.

The PGA allylamines **3.33**–**3.42**, **3.49** and **3.58** showed pleasingly high selectivities in cleavage of the C-N bond of the chiral auxiliary via route *a*. The free primary 1-arylbutylamines (*R*)-**3.64**–**3.74** and (*R*)-**3.82** were obtained in yields up to 95 %. The regioselectivities of cleavage range from 91:9 up to more than 99:1, depending on the substituent. The earlier work of Baltzly and Russel [28c] showed that the electronic nature of the substituent rather than its position is critical in its effect on the regioselectivity of debenzylation. Most substituents studied here are electron-donating and increase the electron density and stability towards cleavage of the *N*-benzyl linkage, promoting cleavage according to route *a*. A third factor that plays a role is steric hindrance, as can be seen in the debenzylation of the phenyl-substituted aryl groups (entries 11-13).

The desired cleavage according to route *a* takes place with phenyl at the *ortho*-position (entry 11) whereas cleavage is almost exclusively via route *b* for phenyl as *meta*- or *para*-substituents (entries 12 and 13). Obviously, the aromatic rings of the biphenyl moiety bind more efficient to the Pd-surface (Eley-Rideal mechanism).[31] A steric effect is doubtlessly present for the case that phenyl is an *ortho*-substituent, yielding the desired arylbutylamine **3.74** as the major product.

Attempts to convert the chloro- and bromo-substituted PGA allylamines **3.43**–**3.48** into the corresponding substituted amines were frustrated by dehalogenation, which occurred prior to debenzylation,[28b,28e] as was established by NMR spectroscopy and mass analysis. In all cases the only product isolated was 1-phenyl-1-butylamine **3.64**.

To our surprise, catalytic hydrogenolysis of the *ortho*-bromo substituted PGA allylamine **3.46** yielded the *ortho*-hydroxy substituted phenylbutylamine **3.79** (Scheme 3.6).



3.46 **3.79**

Scheme 3.6 *Hydrogenolysis of the ortho-bromo substituted PGA homoallylamine **3.46**.*

A possible explanation for this phenomenon could be that the phenylglycine amide acts "pincer-like" as shown in Figure 3.6, in analogy to work described by van Koten *et al*.[32]

Probably an attack of a water molecule or an acetate (followed by hydrolysis) present in the reaction mixture occurs.

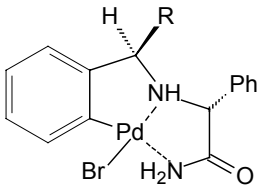
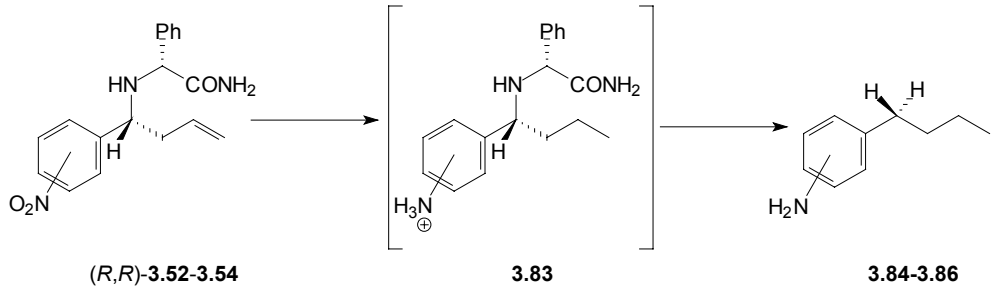


Figure 3.6 *Proposed Pincer-Pd-complex.*

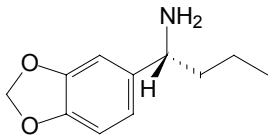
This idea is supported by the fact that this result could not be repeated for the *meta*- and *para*-bromo substituted PGA allylamine under the same conditions. In these cases the only product obtained was the dehalogenated product, (*R*)-1-phenyl-1-butylamine **3.62**. We have not had the opportunity to further investigate this phenomenon in our laboratory.

In the case of the catalytic hydrogenation of the nitro-substituted PGA allylamines (*R*,*R*)-**3.52**–**3.54**, the only products obtained were the aniline-derivatives **3.84**–**3.86** (Scheme 3.7). The NO_2-moiety is reduced prior to debenzylation. Apparently, the electron-withdrawing effect of the cationic NH_3^+ group of intermediate **3.83** [33] weakens the nearby *N*-benzylic bond, resulting in the observed regioselectivity towards **3.84**–**3.86**.

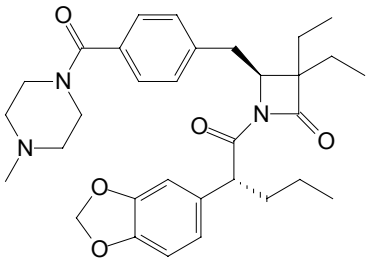


Scheme 3.7 *Regioselectivity of the nitro-substituted PGA allylamines* ***3.52***–***3.54*** *under reductive conditions. Reagents and conditions: i-propanol/H_2O/AcOH, H_2, Pd-C (10 %).*

A demonstration of the synthetic value of this methodology is the preparation of (*R*)-α-3-piperonylbutylamine ((*R*)-**3.82**).[34] This chiral butylamine is an important building block of the human leukocyte elastase inhibitor L-694,458, which was prepared earlier with an enantiomeric excess of 94 % via a three-step reaction sequence.[1c,35]

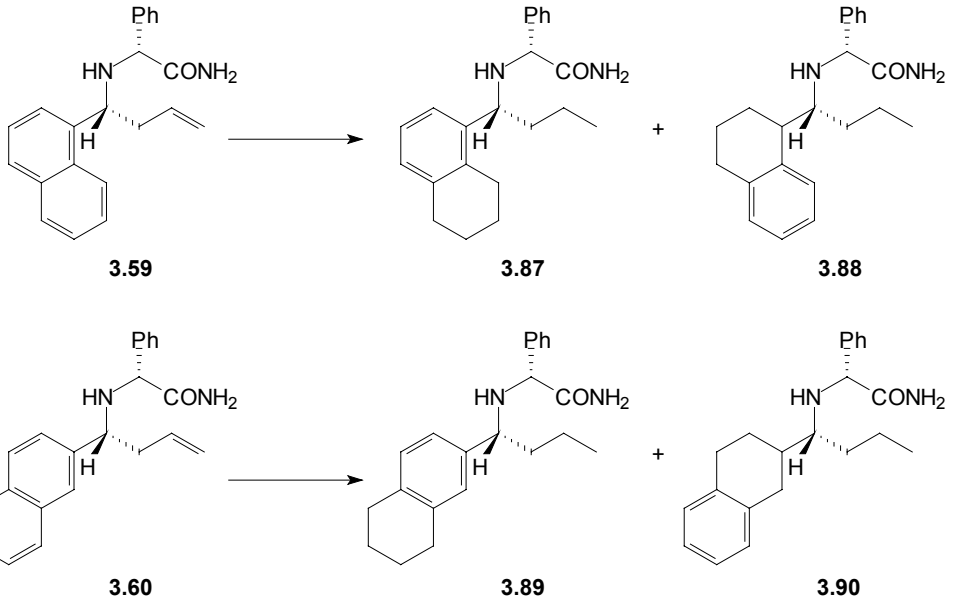


(*R*)-**3.82**



L-694,458

When 1-naphthyl PGA allylamine **3.59** and 2-naphthyl PGA allylamine **3.60** were subjected to analogous hydrogenation conditions, we found reduction of either of the rings of the naphthyl moieties[36] before debenzylation occurred (Scheme 3.8). No further attempts to separate half-products **3.87**–**3.88** or **3.89**–**3.90**, respectively, or further debenzylation have been performed.



3.59 **3.87** **3.88**

3.60 **3.89** **3.90**

Scheme 3.8 *Reduction of the naphthyl moiety of PGA allyl amines **3.59** and **3.60**. Reagents and conditions: i-propanol/H_2O/AcOH, H_2,, Pd-C (10 %).*

In the catalytic hydrogenation of the hydroxy-substituted PGA allylamines **3.55**–**3.57** to remove the benzylic fragment of the chiral PGA auxiliary, the regioselectivity of cleavage towards the desired hydroxy-substituted butylamines **3.78**–**3.59** was poor in all cases (*a:b* > 99:1).

3.5 Conclusions

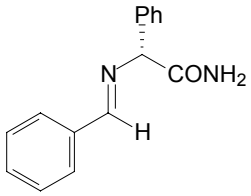
The results presented here illustrate the versatility of (*R*)-phenylglycine amide **3.1** as a readily available chiral auxiliary for the preparation of enantiomerically pure arylbutylamines starting from substituted benzaldehydes. Aldimines derived from (*R*)-PGA are obtained in excellent yield an in high purity. Allylation is readily accomplished in excellent diastereoselectivities with allylzinc bromide, prepared *in situ* from relatively inexpensive allyl bromide. In most cases, the chiral auxiliary is conveniently removed under reductive conditions, with high selectivities of cleavage. In the reduction of the bromo- and chloro-substituted PGA allylamines, dehalogenation is a competing reaction. The sensitivity of the nitro-group prevented the synthesis of the desired nitro-substituted phenylbutylamines using the reductive removal of the chiral auxiliary. Alternative routes to synthesize these compounds, also including the naphthylbutylamines and the hydroxy-substituted phenylbutylamines, will be described in Chapter 4.

Since (*S*)-phenylglycine amide is also available, the opposite configuration of the described products can be generated at will.

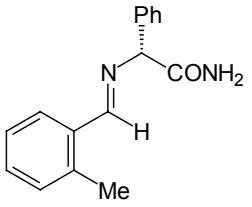
3.6 Experimental Section

General information: Reagents were purchased from Aldrich Chemical Company and were used without further purification. (*R*)-Phenylglycine amide **3.1** was provided by DSM (Geleen, The Netherlands). THF was freshly distilled from benzophenone/sodium. Zinc-wool was cut prior to use or zinc-granules (–30 + 100 mesh) were used. Optical rotations were measured at ambient temperatures using a Perkin-Elmer 241 polarimeter. Melting points were measured on a Büchi B-545 or a Mettler FP1 equipped with a Mettler FP-21 microscope, and are uncorrected. ^{1}H-NMR spectra were recorded on either a Varian AS-400 spectrometer (400MHz), Varian VXR-300 spectrometer (300 MHz) or a Varian Gemini spectrometer (200 MHz). ^{13}C-NMR spectra were recorded on a Varian Gemini 200 (50MHz). Chemical shifts are denoted in parts per million (δ) and are referenced to the residual solvent. Coupling constants *J*, are denoted in Hz and splitting patterns are designated as follows: s (singlet); d (doublet); dd (double doublet); t (triplet); dt (double triplet); q (quartet); m (multiplet) and brs (broad singlet). High resolution mass spectra were recorded on a AEI-MS-902 mass spectrometer by A. Kievit.

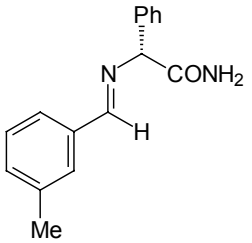
Typical procedure for the synthesis of (*R*)-PGA-aldimines 3.2–3.23. To a suspension of (*R*)-phenylglycine amide **3.1** (30.0 gram, 200 mmol) in CH_2Cl_2 (200 mL) at ambient temperature was added 200 mmol of the substituted benzaldehyde. The reaction mixture was stirred overnight at room temperature. After removal of the CH_2Cl_2 and the water in vaco, the residual solid was washed with acetone/hexane (1:20) and recrystallized once from acetone/hexane (1:20). In all cases exclusively the more stable *E*-isomer was obtained, as judged from the appearance of only one vinyl proton in the ^{1}H-NMR spectrum.



(2*R*)-2-phenyl-2-{[(*E*)-phenylmethylidene]amino} acetamide (3.2): (colorless crystals, 99% yield). m.p. 143.0–144.4 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 4.99 (s, 1H), 6.01 (brs, 1H), 7.03 (brs, 1H), 7.26–7.51 (m, 8H), 7.78–7.83 (m, 2H), 8.31 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 75.45 (d), 125.72 (d), 126.47 (d), 127.00 (d), 127.23 (d), 130.06 (d), 133.89 (s), 137.74 (s), 161.81 (d), 172.67 (s) ppm. Anal. calcd for $C_{15}H_{14}N_2O$: C, 75.61 %; H, 5.92 %; N, 11.76 %. Found: C, 75.61 %; H, 6.02 %; N, 11.65 %. MS (CI): *m/z* = 239 [M + H$^+$].

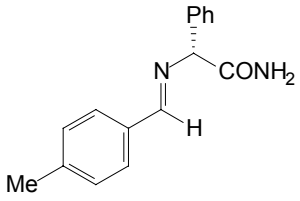


(2*R*)-2-{[(*E*)-(2-methylphenyl)methylidene]amino}-2-phenyl acetamide (3.3): (colorless needles, >99 % yield). m.p. 168.0–168.4 °C. ^{1}H-NMR (200MHz, $CDCl_3$/[D_6]DMSO): δ = 2.53 (s, 3H), 4.99 (s, 1H), 5.91 (brs, 1H), 7.01 (brs, 1H), 7.19-7.53 (m, 8H), 7.95 (dd, *J* = 7.95, *J* = 1.71 Hz, 1H), 8.61 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 17.94 (q), 76.36 (d), 124.95 (d), 126.26 (d), 126.73 (d), 127.23 (d), 129.67 (d), 129.80 (d), 132.44 (s), 137.00 (s), 139.42 (s), 160.26 (d), 171.61 (s) ppm. Anal. calcd. for $C_{16}H_{16}N_2O$: C, 76.16 %; H, 6.39 %; N, 11.10 %. Found: C, 75.78 %; H, 6.37 %; N, 11.09 %. MS (CI): *m/z* = 253 [M + H$^+$].

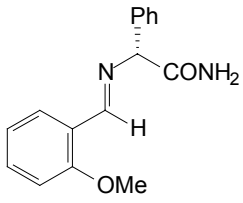


(2*R*)-2-{[(*E*)-(3-methylphenyl)methylidene]amino}-2-phenyl acetamide (3.4): (pale yellow needles, 97 % yield). m.p. 118.0–118.9 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.41 (s, 3H), 4.98 (s, 1H), 5.67 (brs, 1H), 7.05 (brs, 1H), 7.26–7.64 (m, 9H), 8.21 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 18.88 (q), 74.47 (s), 123.46 (s), 124.70 (d), 125.45 (d), 126.14 (d), 126.22 (d), 126.30 (d), 129.88 (d), 132.87 (s), 136.01 (s), 136.74 (s), 161.03 (d), 171.54 (s) ppm. Anal. calcd. for $C_{16}H_{16}N_2O$: C, 75.16 %; H, 6.39 %; N, 11.10 %. Found: C, 75.09 %; H, 6.30 %; N, 11.11 %. MS (CI): *m/z* = 253 [M + H$^+$].

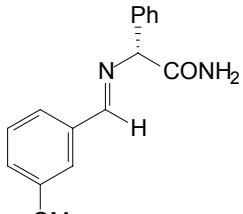
(2*R*)-2-{[(*E*)-(4-methylphenyl)methylidene] amino}-2-phenyl acetamide (3.5): (colorless prisms, >99 % yield). m.p. 153.8–154.0 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.40 (s, 3H), 4.96 (s, 1H), 5.68 (brs, 1H), 7.05 (brs, 1H), 7.22–7.51 (m, 8H), 7.69 (d, J = 7.57 Hz, 2H), 8.27 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 20.10 (q), 75.42 (d), 125.77 (d), 126.40 (d), 126.99 (d), 127.19 (d), 127.95 (d), 131.37 (s), 137.93 (s), 140.50 (s), 161.64 (d), 173.04 (s) ppm. Anal. calcd. for $C_{16}H_{16}N_2O$: C, 75.16 %; H, 6.39 %; N, 11.10 %. Found: C, 76.06 %; H, 6.41 %; N, 11.09 %. MS (CI): *m/z* = 253 (M + H^+).



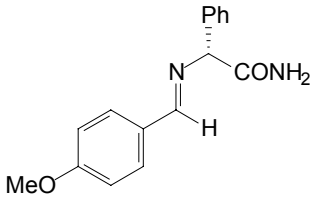
(2*R*)-2-{[(*E*)-(2-methoxyphenyl)methylidene]amino}-2-phenyl acetamide (3.6): (colorless plates, 93 % yield). m.p. 174.3–175.2 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 3.85 (s, 3H), 4.98 (s, 1H), 5.93 (brs, 1H), 6.89–7.04 (m, 3H), 7.26–7.52 (m, 6H), 8.07 (dd, J = 7.57, J = 1.71 Hz, 1H), 8.77 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 54.00 (q), 75.91 (d), 109.66 (d), 119.17 (d), 122.36 (s), 125.67 (d), 125.76 (d), 126.29 (d), 127.14 (d), 131.32 (d), 138.13 (s), 157.65 (s), 157.78 (d), 172.94 (s) ppm. Anal. calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62 %; H, 6.01 %; N, 10.44 %. Found: C, 71.54 %; H, 5.97 %; N, 10.47 %. MS (CI): *m/z* = 269 [M + H^+].



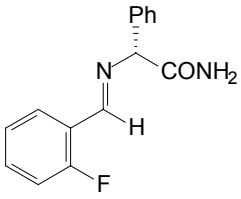
(2*R*)-2-{[(*E*)-(3-methoxyphenyl)methylidene]amino}-2-phenyl acetamide (3.7): (colorless needles, 81 % yield). m.p. 131.9–132.4 °C. ^{1}H-NMR (200MHz, $CDCl_3$/[D_6]DMSO): δ = 3.64 (s, 3H), 4.74 (s, 1H), 6.07 (brs, 1H), 6.78–6.82 (m, 2H), 6.88 (brs, 1H), 7.04–7.27 (m, 6H), 8.07 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 55.37 (q), 76.87 (d), 112.55 (d), 117.61 (d), 126.98 (d), 127.20 (d), 127.95 (d), 128.71 (d), 129.75 (d), 136.76 (s), 139.15 (s), 159.87 (s), 163.18 (d), 174.07 (s) ppm. Anal. calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62 %; H, 6.01 %; N, 10.44 %. Found: C, 71.62 %; H, 6.09 %; N, 10.41 %. MS (CI): *m/z* = 269 [M + H^+].



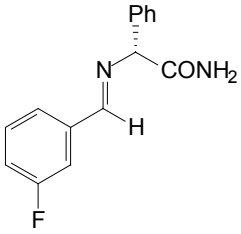
(2*R*)-2-{[(*E*)-(4-methoxyphenyl)methylidene] amino}-2-phenyl acetamide (3.8): (yellow solid, 98 % yield). m.p. 92.5–93.3 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 3.85 (s, 3H), 4.94 (s, 1H), 5.81 (brs, 1H), 6.95 (d, J = 8.79 Hz, 2H), 7.06 (brs, 1H), 7.26–7.50 (m, 5H), 7.75 (d, J = 8.79 Hz, 2H), 8.23 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 53.92 (q), 75.37 (d), 112.60 (d), 125.75 (d), 126.35 (d), 126.91 (s), 127.17 (d), 128.66 (d), 138.05 (s), 160.77 (s), 160.99 (d), 173.13 (s) ppm. Anal.



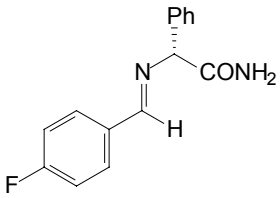
calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62 %; H, 6.01 %; N, 10.44 %. Found: C, 71.30 %; H, 5.95 %; N, 10.44 %. MS (CI): *m/z* = 269 [M + H^+].



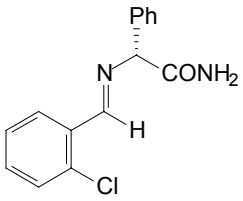
(2*R*)-2-{[(*E*)-(2-fluorophenyl)methylidene]amino}-2-phenyl acetamide (3.9): (pale yellow needles, 97 % yield). m.p. 153.7–154.2 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 4.80 (s, 1H), 6.28 (brs, 1H), 6.80 (brs, 1H), 6.91 (t, *J* = 9.34 Hz, 1H), 7.04 (t, *J* = 7.33 Hz, 1H), 7.10–7.30 (m, 6H), 7.90 (t, *J* = 7.33 Hz, 1H), 8.43 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 74.95 (d), 113.39 (d, $^2J_{C\text{-}F}$ = 21.98 Hz), 120.52 (s, $^2J_{C\text{-}F}$ = 9.76 Hz), 121.83 (d, $^3J_{C\text{-}F}$ = 3.67Hz), 124.65 (d), 125.24 (d, $^4J_{C\text{-}F}$ = 2.44 Hz), 125.35 (d), 126.11 (d), 130.66 (d, $^3J_{C\text{-}F}$ = 9.77 Hz), 136.69 (s), 154.00 (d, $^3J_{C\text{-}F}$ = 4.88 Hz), 159.82 (s, $^1J_{C\text{-}F}$ = 253.92 Hz), 171.12 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OF$: C, 70.30 %; H, 5.10 %; N, 10.90 %. Found: C, 70.40 %; H, 5.04 %; N, 10.87 %. MS (CI): *m/z* = 257 [M + H^+].



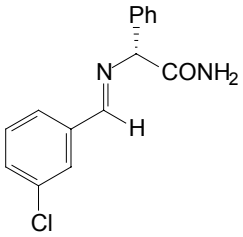
(2*R*)-2-{[(*E*)-(3-fluorophenyl)methylidene]amino}-2-phenyl acetamide (3.10): (yellow plates, 96 % yield). m.p. 121.6–121.9 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 4.71 (s, 1H), 6.39 (brs, 1H), 6.74 (brs, 1H), 6.91 (dd, *J* = 8.24 Hz, 1H), 7.02–7.28 (m, 7H), 7.34 (d, *J* = 9.16 Hz, 1H), 8.04 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 74.42 (d), 111.55 (d, $^2J_{C\text{-}F}$ = 23.20 Hz), 115.73 (d, $^2J_{C\text{-}F}$ = 20.76 Hz), 122.32 (d, $^3J_{C\text{-}F}$ = 2.44 Hz), 124.64 (d), 125.27 (d), 126.05 (d), 127.73 (d, $^3J_{C\text{-}F}$ = 7.32 Hz), 135.09 (s, $^3J_{C\text{-}F}$ = 7.32 Hz), 136.65 (s), 159.14 (d, $^4J_{C\text{-}F}$ = 2.44 Hz), 160.26 (s, $^1J_{C\text{-}F}$ = 246.60 Hz), 170.92 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OF$: C, 70.30 %; H, 5.11 %; N, 10.93 %. Found: C, 70.00 %; H, 5.23 %; N, 10.81 %. MS (CI): *m/z* = 257 [M + H^+].



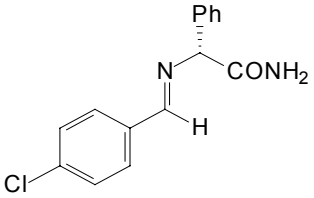
(2*R*)-2-{[(*E*)-(4-fluorophenyl)methylidene]amino}-2-phenyl acetamide (3.11): (colorless plates, 95 % yield). m.p. 119.4–120.5 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 4.98 (s, 1H), 5.85 (brs, 1H), 6.96 (brs, 1H), 7.09–7.50 (m, 10H), 7.77–7.84 (m, 2H), 8.28 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 75.42 (d), 114.20 (d), 114.42 (d, $^2J_{C\text{-}F}$ = 21.72 Hz), 125.70 (d), 126.53 (d), 127.26 (d), 128.90 (d), 128.98 (d, $^3J_{C\text{-}F}$ = 8.75 Hz), 130.16 (s), 137.64 (s), 160.39 (d), 163.25 (s, $^1J_{C\text{-}F}$ = 252.51 Hz), 172.55 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OF$: C, 70.30 %; H, 5.10 %; N, 10.90 %. Found: C, 70.38 %; H, 5.14 %; N, 10.83 %. MS (CI): *m/z* = 257 [M + H^+].



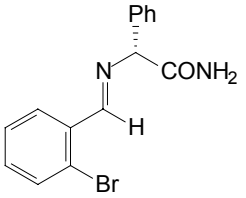
(2*R*)-2-{[(*E*)-(2-chlorophenyl)methylidene]amino}-2-phenyl acetamide (3.12): (colorless needles, 97 % yield). m.p. 170.3–171.0 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 5.05 (s, 1H), 6.20 (brs, 1H), 6.94 (brs, 1H), 7.26-7.51 (m, 8H), 8.13 (d, J = 6.10 Hz, 1H), 8.76 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 75.84 (d), 125.52 (d), 125.68 (d), 126.56 (d), 126.87 (d), 127.28 (d), 128.56 (d), 130.87 (d), 134.53 (s), 137.85 (s), 158.65 (d), 172.42 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OCl$: C, 66.05 %; H, 4.80 %; N, 10.27 %. Found: C, 65.92 %; H, 4.81 %; N, 10.31 %. MS (CI): *m/z* = 273 (100.0) [M + H$^+$], 275 (34.5) [M + H$^+$].



(2*R*)-2-{[(*E*)-(3-chlorophenyl)methylidene]amino}-2-phenyl acetamide (3.13): (colorless plates, 98 % yield). m.p. 119.4–120.9 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 4.94 (s, 1H), 5.83 (brs, 1H), 6.90 (brs, 1H), 7.21–7.42 (m, 7H), 7.56 (d, J = 7.33 Hz, 1H), 7.80 (s, 1H), 8.29 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 76.90 (d), 127.08 (d), 127.16 (d), 127.77 (d), 128.08 (d), 128.78 (d), 129.99 (d), 124.94 (s), 131.46 (d), 137.03 (s), 138.86 (s), 161.88 (d), 173.64 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OCl$: C, 66.05 %; H, 4.80 %; N, 10.27 %. Found: C, 65.77 %; H, 4.89 %; N, 10.36 %. MS (CI): *m/z* = 273 (100.0) [M + H$^+$], 275 (36.1) [M + H$^+$].

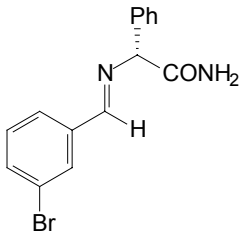


(2*R*)-2-{[(*E*)-(4-chlorophenyl)methylidene] amino}-2-phenyl acetamide (3.14): (pale yellow plates, 95 % yield). m.p. 153.4–154.2 °C. ^{1}H-NMR (200MHz, $CDCl_3$/[D_6]DMSO): δ = 4.83 (s, 1H), 6.28 (brs, 1H), 6.83 (brs, 1H), 7.14–7.36 (m, 7H), 7.63 (d, J = 8.55 Hz, 2H), 8.15 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 75.49 (d), 125.65 (d), 126.34 (d), 127.10 (d), 127.38 (d), 128.11 (d), 132.31 (s), 135.80 (s), 137.66 (s), 160.23 (d), 172.09 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OCl$: C, 66.05 %; H, 4.80 %; N, 10.27 %. Found: C, 65.76 %; H, 4.93 %; N, 10.25 %. MS (CI): *m/z* = 273 (100.0) [M + H$^+$], 275 (34.8) [M + H$^+$].

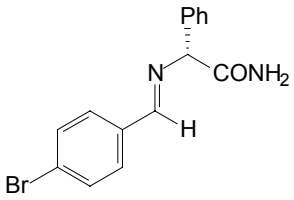


(2*R*)-2-{[(*E*)-(2-bromophenyl)methylidene]amino}-2-phenyl acetamide (3.15): (pale yellow needles, 99 % yield). m.p. 168.3–168.7 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 5.02 (s, 1H), 5.22 (brs, 1H), 6.88 (brs, 1H), 7.21-7.36 (m, 5H), 7.43 (d, J = 6.95 Hz, 2H), 7.54 (dd, J = 8.06 Hz, 1H), 8.07 (dd, J = 7.69, J = 1.83 Hz, 1H), 8.65 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 76.54 (d), 124.57 (s), 127.43 (d), 127.47 (d), 128.00 (d), 128.36 (d), 129.30 (d), 132.94 (d), 133.07 (d), 133.73 (s), 140.01 (s), 160.90 (d), 172.20 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OBr$: C, 56.80 %; H, 4.13 %; N, 8.83%.

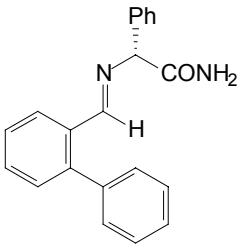
Found: C, 56.89 %; H, 4.22 %; N, 9.08 %. MS (CI): *m/z* = 317 (100.0) [M + H^+], 319 (98.3) [M + H^+].

(2*R*)-2-{[(*E*)-(3-bromophenyl)methylidene]amino}-2-phenyl acetamide (3.16): 

(colorless plates, 98 % yield). m.p. 135.0–136.3 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 4.94 (s, 1H), 5.68 (brs, 1H), 6.90 (brs, 1H), 7.20–7.33 (m, 5H), 7.41 (d, *J* = 6.95 Hz, 1H), 7.54 (d, *J* = 8.61 Hz, 1H), 7.61 (d, *J* = 7.69 Hz, 1H), 7.96 (s, 1H), 8.20 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 74.45 (d), 120.54 (s), 124.73 (d), 125.06 (d), 125.62 (d), 126.32 (d), 127.28 (d), 128.28 (d), 131.89 (d), 134.81 (s), 136.42 (s), 159.29 (d), 171.36 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OBr$: C, 56.80 %; H, 4.13 %; N, 8.83 %. Found: C, 56.65 %; H, 4.12 %; N, 8.82 %. MS (CI): *m/z* = 317 (100.0) [M + H^+], 319 (99.3) [M + H^+].

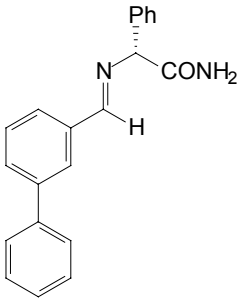
(2*R*)-2-{[(*E*)-(4-bromophenyl)methylidene]amino}-2-phenyl acetamide (3.17): 

(colorless prisms, 99 % yield). m.p. 164.0–165.3 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 4.68 (s, 1H), 6.37 (brs, 1H), 6.69 (brs, 1H), 6.98–7.21 (m, 5H), 7.27 (d, *J* = 8.44 Hz, 2H), 7.43 (d, *J* = 8.44 Hz, 2H), 8.01 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 74.43 (d), 123.02 (s), 124.59 (d), 125.12 (d), 125.90 (d), 127.26 (d), 129.15 (d), 131.71 (s), 136.71 (s), 159.11 (d), 170.81 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_2OBr$: C, 56.80 %; H, 4.13 %; N, 8.83 %. Found: C, 56.70 %; H, 4.22 %; N, 8.86 %. MS (CI): *m/z* = 317 (97.8) [M + H^+], 319 (100.0) [M + H^+].

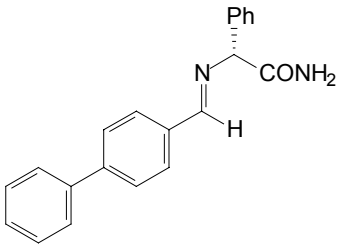
(2*R*)-2-{[(*E*)-[1,1'-biphenyl]-2-ylmethylidene]amino}-2-phenyl acetamide (3.18): 

(white solid, 85 % yield). m.p. 152.4–152.6 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 4.55 (s, 1H), 6.27 (brs, 1H), 6.81 (brs, 1H), 6.97–7.92 (m, 14H), 7.95 (d, *J* = 6.22 Hz, 1H), 8.02 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 76.58 (d), 127.16 (d), 127.30 (d), 127.30 (d), 127.76 (d), 127.83 (d), 128.13 (d), 129.28 (d), 129.86 (s), 130.42 (d), 132.36 (s), 138.52 (s), 139.03 (s), 143.01 (s), 161.92 (d), 173.48 (s) ppm. Anal. calcd. for $C_{21}H_{18}N_2O$: C, 80.23 %; H, 5.77 %; N, 8.91 %. Found: C, 80.02 %; H, 5.71 %; N, 8.91 %. MS (CI): *m/z* = 315 [M + H^+].

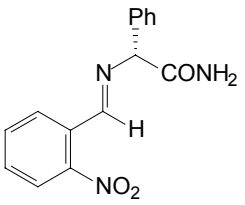
(2*R*)-2-{[(*E*)-[1,1'-biphenyl]-3-ylmethylidene]amino}-2-phenyl acetamide (3.19): (white solid, 89 % yield). m.p. 145.7–146.4 °C. ^{1}H NMR (300MHz, $CDCl_3$): δ = 4.99 (s, 1H), 6.78 (brs, 1H), 7.04 (brs, 1H), 7.24–7.49 (m, 11H), 7.59 (dd, *J* = 6.59, *J* = 1.10 Hz, 2H), 7.66 (d, *J* = 6.59 Hz, 1H), 7.73 (d, *J* = 6.59 Hz, 1H), 7.99 (d, *J* = 1.10 Hz, 1H), 8.31 (s, 1H) ppm. ^{13}C NMR (50MHz, $CDCl_3$): δ = 76.79 (d), 126.85 (d), 126.93 (d), 127.01 (d), 127.20 (d), 127.32 (d), 127.59 (d), 127.82 (d), 128.60 (d), 128.76 (d), 129.03 (d), 130.08 (d), 135.76 (s), 139.13 (s), 140.13 (s), 141.64 (s), 163.12 (d), 174.46 (s) ppm. Anal. calcd. for $C_{21}H_{18}N_2O$: C, 80.23 %; H, 5.77 %; N, 8.91 %. Found: C, 80.29 %; H, 5.82 %; N, 8.84 %. MS (CI): *m/z* = 315 [M + H^+].

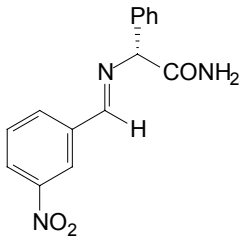


(2*R*)-2-{[(*E*)-[1,1'-biphenyl]-4-ylmethylidene] amino}-2-phenyl acetamide (3.20): (white solid, 95 % yield). m.p. 176.5–177.0 °C. ^{1}H NMR (300MHz, $CDCl_3$): δ = 4.96 (s, 1H), 5.79 (brs, 1H), 7.00 (brs, 1H), 7.24–7.25 (m, 2H), 7.31 (t, *J* = 7.33 Hz, 2H), 7.36–7.46 (m, 4H), 7.57 (d, *J* = 7.33 Hz, 2H), 7.62 (d, *J* = 8.06 Hz, 2H), 7.82 (d, *J* = 8.06 Hz, 2H), 8.30 (s, 1H) ppm. ^{13}C NMR (50MHz, $CDCl_3$): δ = 76.68 (d), 126.58 (d), 126.80 (d), 127.33 (d), 127.46 (d), 128.15 (d), 128.43 (d), 128.50 (d), 129.75 (s), 139.08 (s), 139.52 (s), 143.54 (s), 162.17 (d), 173.49 (s) ppm. Anal. calcd. for $C_{21}H_{18}N_2O$: C, 80.23 %; H, 5.77 %; N, 8.91 %. Found: C, 80.35 %; H, 5.84 %; N, 8.88 %. MS (CI): *m/z* = 315 [M + H^+].

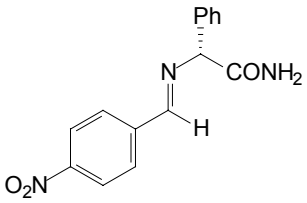


(2*R*)-2-{[(*E*)-(2-nitrophenyl)methylidene]amino}-2-phenyl acetamide (3.21): (pale yellow needles, 97 % yield). m.p. 165.0–165.4 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 4.90 (s, 1H), 6.43 (brs, 1H), 6.73 (brs, 1H), 7.14–7.23 (m, 3H), 7.31 (d, *J* = 6.96 Hz, 2H), 7.48 (dt, *J* = 7.46 Hz, 1H), 7.56 (dt, *J* = 7.46 Hz, 1H), 7.83 (dd, *J* = 7.46, *J* = 0.72 Hz, 1H), 7.92 (dd, *J* = 7.46, *J* = 0.72 Hz, 1H), 8.55 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 76.90 (d), 123.91 (d), 126.92 (d), 127.68 (d), 128.38 (d), 129.53 (s), 129.73 (d), 131.18 (d), 132.99 (d), 138.34 (s), 148.46 (s), 158.69 (d), 172.75 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60 %; H, 4.63 %; N, 14.83 %. Found: C, 63.55 %; H, 4.57 %; N, 14.78 %. MS (CI): *m/z* = 284 [M + H^+].

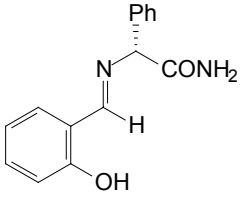




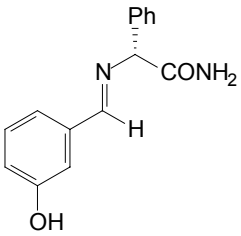
(2*R*)-2-{[(*E*)-(3-nitrophenyl)methylidene]amino}-2-phenyl acetamide (3.22): (pale yellow plates, 98 % yield). m.p. 174.0–174.9 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 4.73 (s, 1H), 6.50 (brs, 1H), 6.72 (brs, 1H), 6.96–7.07 (m, 3H), 7.16-7.21 (m, 2H), 7.35 (t, J = 7.97 Hz, 1H), 7.83 (dd, J = 7.97, J = 1.81 Hz, 1H), 7.99 (dd, J = 7.97, J = 1.81 Hz, 1H), 8.13 (s, 1H), 8.38 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 75.84 (d), 121.42 (d), 124.28 (d), 125.96 (d), 126.65 (d), 127.36 (d), 128.55 (d), 133.10 (d), 135.70 (s), 137.67 (s), 147.12 (s), 159.37 (d), 171.73 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60 %; H, 4.63 %; N, 14.83 %. Found: C, 63.50 %; H, 4.84 %; N, 14.79 %. MS (CI): m/z = 284 [M + H$^+$].



(2*R*)-2-{[(*E*)-(4-nitrophenyl)methylidene]amino}-2-phenyl acetamide (3.23): (pale yellow prisms, 92 % yield). m.p. 168.1–168.3 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 5.07 (s, 1H), 5.81 (brs, 1H), 6.86 (brs, 1H), 7.30–7.46 (m, 3H), 7.98 (d, J = 8.79 Hz, 2H), 8.30 (d, J = 8.79 Hz, 2H), 8.41 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 77.27 (d), 124.01 (d), 127.21 (d), 128.35 (d), 128.95 (d), 129.22(d), 138.47 (s), 140.57 (s), 149.51 (s), 161.21 (d), 173.06 (s) ppm. Anal. calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60 %; H, 4.63 %; N, 14.83 %. Found: C, 63.36 %; H, 4.62 %; N, 14.83 %. MS (CI): m/z = 284 [M + H$^+$].



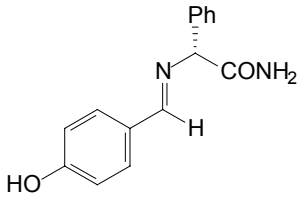
(2R)-2-{[(*E*)-(2-hydroxyphenyl)methylidene]amino}-2-phenyl acetamide (3.24): (colorless plates, 97 % yield). m.p. 147.1–148.2 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 5.05 (s, 1H), 5.73 (brs, 1H), 6.12 (brs, 1H), 6.89–7.02 (m, 2H), 7.26–7.49 (m, 7H), 8.45 (s, 1H), 12.45 (brs, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 75.70 (d), 115.56 (d), 116.96 (s), 117.84 (d), 125.74 (d), 126.98 (d), 127.58 (d), 130.81 (d), 131.92 (d), 136.23 (s), 159.06 (s), 166.33 (d), 171.04 (s) ppm. Anal. calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85 %; H, 5.55 %; N, 11.02 %. Found: C, 70.57 %; H, 5.57 %; N, 10.92 %. MS (CI): m/z = 255 [M + H$^+$].



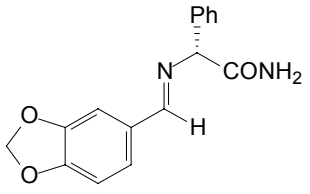
(2R)-2-{[(*E*)-(3-hydroxyphenyl)methylidene]amino}-2-phenyl acetamide (3.25): (pale yellow plates, 98 % yield). m.p. 146.2–147.2 °C. ^{1}H-NMR (300MHz, $CDCl_3$/ [D_6]DMSO): δ = 4.57 (s, 1H), 6.44 (brs, 1H), 6.60 (d, J = 3.29 Hz, 1H), 6.69 (brs, 1H), 6.88–7.20 (m, 8H), 7.89 (s, 1H), 8.85 (brs, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/ [D_6]DMSO): δ = 80.28 (d), 117.93 (d), 122.19 (d), 123.30 (d), 130.54 (d), 130.98 (d), 131.79 (d), 132.89 (d), 139.99 (s), 142.92 (s), 160.94 (s), 166.33 (d), 177.19 (s) ppm. Anal. calcd. for

$C_{15}H_{14}N_2O_2$: C, 70.85 %; H, 5.55 %; N, 11.02 %. Found: C, 70.52 %; H, 5.57 %; N, 10.94 %. MS (CI): *m/z* = 255 [M + H^+].

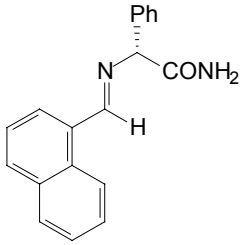
(2R)-2-{[(*E*)-(4-hydroxyphenyl)methylidene] amino}-2-phenyl acetamide (3.26): (colorless crystals, 92 % yield). m.p. 132.5–132.9 °C. ^{1}H-NMR (200MHz, $CDCl_3$/ [D_6]DMSO): δ = 4.70 (s, 1H), 6.24 (brs, 1H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.89 (brs, 1H), 7.05–7.28 (m, 5H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.99 (s, 1H), 9.31 (brs, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/ [D_6]DMSO): δ = 74.34 (d), 113.07 (d), 124.39 (s), 124.60 (d), 124.93 (d), 125.80 (d), 127.55 (d), 137.34 (s), 157.98 (s), 159.76 (d), 171.54 (s) ppm. Anal. calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85 %; H, 5.55 %; N, 11.02 %. Found: C, 70.52 %; H, 5.57 %; N, 10.94 %. MS (CI): *m/z* = 255 [M + H^+].



(2*R*)-2-{[(*E*)-1,3-benzodioxol-5-ylmethylidene] amino}-2-phenyl acetamide (3.27): To a suspension of (*R*)-phenylglycine amide (15.0 gram, 100 mmol) in $CHCl_3$, was added piperonal (15.0 gram, 100 mmol) and a catalytic amount of *p*-TolSO_3H (0.3 g). The mixture was refluxed for 2 hours. Magnesium sulphate was added and the mixture was filtered. The filtrate was evaporated and the residue was recrystallized from diethyl ether. (colorless powder, 85 % yield). m.p. 138.0–139.0 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.94, (s, 1H), 5.86 (brs, 1H), 6.02 (s, 1H), 6.03 (s, 1H), 6.81–6.86 (m, 1H), 7.00 (brs, 1H), 7.11–7.16 (m, 1H), 7.26–7.49 (m, 6H), 8.17 (s, 1H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 75.24 (d), 100.14 (t), 104.97 (d), 106.64 (d), 123.94 (d), 125.79 (d), 126.39 (d), 127.20 (s), 128.78 (s), 138.03 (d), 146.56 (s), 149.04 (s), 160.79 (d), 173.19 (s) ppm. Anal. calcd for $C_{16}H_{14}N_2O_3$: C, 68.08 %; H, 5.00 %; N, 9.92 %. Found: C, 67.74 %; H, 5.07 %; N, 9.97 %. MS (CI): *m/z* = 283 [M + H^+].

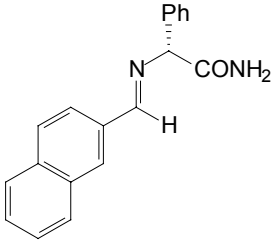


(2*R*)-2-{[(*E*)-1-naphthylmethylidene]amino}-2-phenyl acetamide (3.28): Recrystallized from acetone/hexane (1:20). (white needles, 83 % yield). m.p. 166.5–166.8 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 5.04 (s, 1H), 5.59 (brs, 1H), 6.96 (brs, 1H), 7.27 (d, *J* = 7.32 Hz, 1H), 7.34 (t, *J* = 7.32 Hz, 2H), 7.47–7.60 (m, 5H), 7.86 (d, *J* = 8.05 Hz, 1H), 7.92 (t, *J* = 6.59 Hz, 2H), 8.83 (d, *J* = 8.32 Hz, 1H), 8.92 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 77.97 (d), 123.40 (d), 124.69 (d), 125.74 (d), 126.81 (d), 127.03 (d), 127.36 (d), 128.20



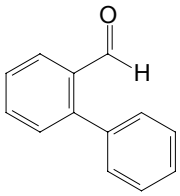
(d), 128.30 (d), 129.26 (d), 130.14 (s), 130.66 (s), 131.46 (d), 133.24 (s), 139.12 (s), 162.49 (d), 173.48 (s) ppm. Anal. calcd for $C_{19}H_{16}N_2O$: C, 79.14 %; H, 5.59 %; N, 9.72 %. Found: C, 78.74 %; H, 5.59 %; N, 9.64 %. MS (CI): *m/z* = 289 [M + H^+].

(2*R*)-2-{[(*E*)-2-naphthylmethylidene]amino}-2-phenyl acetamide (3.29): (white solid, 91% yield) m.p. 179.6–182.0 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 5.06 (s, 1H), 7.26-7.43 (m, 6H), 7.51 (d, *J* = 7.69 Hz, 1H), 7.57–7.60 (m, 2H), 7.97–8.03 (m, 3H), 8.20 (d, *J* = 8.42 Hz, 1H), 8.27 (s, 1H), 8.60 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 76.84 (d), 126.78 (d), 127.49 (d), 127.85 (d), 128.34 (d), 128.41 (d), 128.69 (d), 130.69 (d), 132.65 (s), 133.48 (s), 134.42 (s), 140.39 (s), 162.62 (d), 172.77 (s) ppm. MS (CI): *m/z* = 289 [M^+ + H^+].

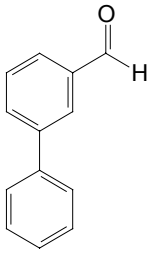


Typical procedure for the preparation of phenyl-substituted benzaldehydes 3.30–3.32 via a Pd–C catalyzed Suzuki coupling. A solution of sodium carbonate (17.88 gram, 168.7 mmol, 1.25 equiv.) in water (100 mL) was added carefully to a stirred suspension of 25.00 gram 2-bromobenzaldehyde (135 mmol, 1.0 equiv.), phenylboronic acid (18.13 gram, 149 mmol, 1.1 equiv.), 10 % palladium on charcoal (2.67 mmol, 2 mol %) in *i*–propanol (30 mL) and water (100 mL). The reaction was stirred for two days at 65 °C,[20] then it was cooled to ambient temperature and diluted with 70:15:1 *i*–propanol/H_2O/2N NaOH solution (50 mL). The catalyst was removed by filtration under suction of the reaction mixture over Celite and the residue was washed with the same solvent mixture (3 × 50 mL). The *i*–propanol was removed in vacuo and the residual mixture was extracted with dichloromethane (3 × 30 mL). The aqueous phase was neutralized with 10 % HCl and extracted with dichloromethane (3 × 30 mL) and with diethyl ether (3 × 30 mL). The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent yielded the biaryl compounds **3.30**–**3.32** as the only products.

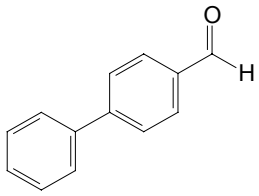
[1,1'-Biphenyl]-2-carboxaldehyde (3.30): (yellow oil, 93 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 7.31–7.34 (m, 2H), 7.38–7.46 (m, 5H), 7.58 (dt, *J* = 7.69, *J* = 1.47 Hz, 1H), 7.99 (dd, *J* = 7.69, *J* = 1.10 Hz, 1H), 9.94 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 127.42 (d), 127.64 (d), 127.99 (d), 128.30 (d), 129.97 (d), 130.65 (d), 133.44 (d), 133.55 (s), 137.58 (s), 145.81 (s), 192.28 (d) ppm. Anal. calcd for $C_{13}H_{10}O$: C, 85.69 %; H, 5.53 %. Found: C, 85.61 %; H, 5.45 %. MS (CI): *m/z* = 183 [M + H^+].



[1,1'-Biphenyl]-3-carboxaldehyde (3.31): (yellow oil, 94 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 7.35–7.45 (m, 3H), 7.53–7.58 (m, 3H), 7.77–7.81 (m, 2H), 8.05 (s, 1H), 10.02 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 126.92 (d), 127.84 (d), 127.93 (d), 128.42 (d), 128.82 (d), 129.29 (d), 132.79 (d), 136.72 (s), 139.42 (s), 141.86 (s), 192.08 (d) ppm. Anal. calcd for $C_{13}H_{10}O$: C, 85.69 %; H, 5.53 %. Found: C, 85.38 %; H, 5.57 %. MS (CI): *m/z* = 183 [M + H^+].

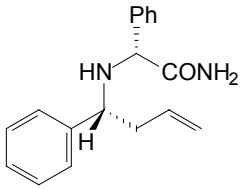


[1,1'-Biphenyl]-4-carboxaldehyde (3.32): (white solid, 95 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 7.34–7.47 (m, 3H), 7.59 (dd, *J* = 9.05, *J* = 1.28 Hz, 2H), 7.70 (d, *J* = 9.25 Hz, 2H), 7.90 (d, *J* = 9.25 Hz, 2H), 10.00 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 127.35 (d), 127.67 (d), 128.45 (d), 129.00 (d), 130.25 (d), 135.18 (s), 139.70 (s), 147.19 (s), 191.91 (d) ppm. Anal. calcd for $C_{13}H_{10}O$: C, 85.69 %; H, 5.53 %. Found: C, 85.50 %; H, 5.55 %. MS (CI): *m/z* = 183 [M + H^+].

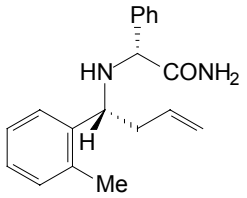


Typical procedure for the allylation of (*R*)-PGA imines 3.2–3.29. A solution of allylzinc bromide (1.5 equiv.) was prepared by adding allyl bromide (38.5 mL, 438 mmol) to finely cut zinc-wool (28.6 gram, 438 mmol) in THF (250 mL). The solution of allylzinc bromide was cooled to 0 °C and the imine (292 mmol) in THF (150 mL) was added batch-wise maintaining this temperature. The reaction mixture was allowed to warm to room temperature and was then poured into water (500 mL). Ethyl acetate (200 mL) was added and the mixture was stirred vigorously. After filtration over Celite, the organic phase was separated and the water layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulphate and concentrated in vacuo to furnish the homoallylamine as a colorless oil, which in almost all cases crystallized on standing In all cases, the *dr* could be increased to more than 99:1 by recrystallization from acetone/hexane (1:20).

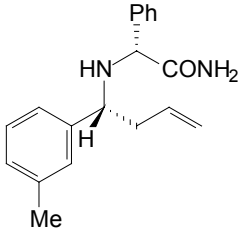
Typical procedure for the allylation of (*R*)-PGA imines 3.2–3.11, 3.18–3.20 and 3.28–3.29 under Barbier conditions. To a flask, fitted with a cooler and charged with THF (250 mL) was added successively the imine (292 mmol) and zinc-wool (28.6 gram, 438 mmol). To the stirred mixture was added allyl bromide (438 mmol, 38.5 mL, 1.5 equiv.) in 50 mL THF at 0 ^{o}C. The reaction mixture was allowed to warm to ambient temperature. Work-up was performed as described above.



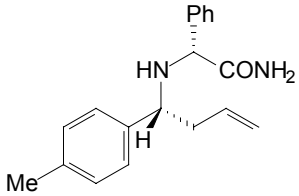
(2R)-2-phenyl-2-{[(1*R*)-1-phenyl-3-butenyl]amino} ethanamide (3.33): (colorless crystals, >99 % yield, >99:1 *dr*) m.p. 89.0–90.0 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.41 (dd, J = 6.96 Hz, 2H), 3.69 (t, J = 6.96 Hz, 1H), 3.95 (s, 1H), 5.01-5.09 (m, 2H), 5.66–5.78 (m, 1H), 6.95 (brs, 1H), 7.05 (brs, 1H), 7.14–7.31 (m, 10H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 40.09 (t), 59.19 (d), 61.83 (d), 115.35 (t), 124.64 (d), 124.83 (d), 125.01(d), 125.59 (d), 126.16 (d), 126.35 (d), 132.50 (d), 136.90 (s), 140.19 (s), 173.67 (s) ppm. Anal. calcd for $C_{18}H_{20}N_2O$: C, 77.11 %; H, 7.19 %; N, 9.99 %. Found: C, 76.95 %; H, 7.22 %; N, 9.92 %. MS (CI): *m/z* = 281 [M + H^+].



(2*R*)-2-{[(1*R*)-1-(2-methylphenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.34): (colorless plates, 93 % yield, 99:1 *dr*). m.p. 104.3–104.6 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.25 (s, 3H), 2.31-2.37 (m, 1H), 3.89 (s, 1H), 4.01 (d, J = 6.23 Hz, 1H), 5.02–5.11 (m, 2H), 5.68-5.82 (m, 1H), 6.12 (brs, 1H), 7.10–7.25 (m, 10H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 16.95 (q), 39.32 (t), 54.21 (d), 61.96 (d), 115.32 (t), 122.53 (d), 123.93 (d), 124.49 (d), 124.77 (d), 125.62 (d), 126.35 (d), 128.12 (d), 132.53 (d), 133.65 (s), 136.89 (s), 138.26 (s), 173.53 (s) ppm. Anal. calcd for $C_{19}H_{22}N_2O \cdot ½\ H_2O$: C, 75.22 %; H, 7.64 %; N, 9.23 %. Found: C, 75.18 %; H, 7.59 %; N, 9.12 %. MS (CI): *m/z* = 295 [M + H^+].

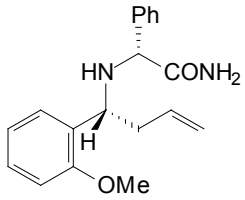


(2*R*)-2-{[(1*R*)-1-(3-methylphenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.35): (yellow oil, >99 % yield, >99:1 *dr*). m.p. 79.0–80.3 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.11 (brs, 1H), 2.30 (s, 3H), 2.39 (d, J = 6.96 Hz, 2H), 3.65 (t, J = 6.96 Hz, 1H), 3.96 (s, 1H), 5.03–5.10 (m, 2H), 5.69–5.83 (m, 1H), 6.96–7.06 (m + brs, 3H), 7.11 (brs, 1H), 7.16–7.29 (m, 7H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 18.60 (q), 42.35 (t), 61.53 (d), 64.17 (d), 117.45 (t), 123.76 (d), 127.07 (d), 127.69 (d), 127.82 (d), 127.98 (d), 128.28 (d), 128.58 (d), 134.87 (d), 137.93 (s), 139.26 (s), 142.40 (s), 175.88 (s) ppm. Anal. calcd for $C_{19}H_{22}N_2O \cdot ½\ H_2O$: C, 75.22 %; H, 7.64 %; N, 9.23 %. Found: C, 75.52 %; H, 7.45 %; N, 9.35 %. MS (CI): *m/z* = 295 [M + H^+].

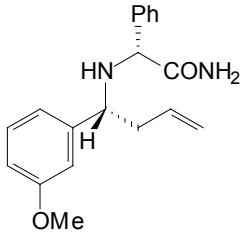


(2*R*)-2-{[(1*R*)-1-(4-methylphenyl)-3-butenyl] amino}-2-phenyl ethanamide (4.36): (colorless oil, which crystallizes on standing, 97 % yield, >99:1 *dr*). m.p. 120.3–121.4 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.04 (brs, 1H), 2.30 (s, 3H), 2.38 (d, J = 6.96 Hz, 2H), 3.63 (t, J = 6.96 Hz, 1H), 3.95 (s, 1H), 5.01–5.08 (m, 2H), 5.67–5.81 (m, 1H), 6.12 (brs, 1H),

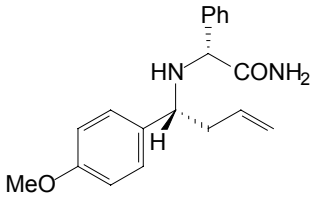
7.05–7.11 (m, 5H), 7.16–7.24 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 18.60 (q), 40.04 (t), 58.96 (d), 61.86 (d), 115.22 (t), 124.42 (d), 124.75 (d), 125.61 (d), 126.33 (d), 126.80 (d), 132.56 (d), 134.59 (s), 136.81 (s), 136.92 (s), 173.67 (s) ppm. Anal. calcd for $C_{19}H_{22}N_2O$: C, 77.52 %; H, 7.53 %; N, 9.52 %. Found: C, 77.43 %; H, 7.42 %; N, 9.34 %. MS (CI): *m/z* = 295 [M + H$^+$].



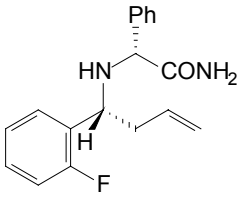
(2*R*)-2-{[(1*R*)-1-(2-methoxyphenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.37): (pale yellow solid, 98 % yield, >99:1 *dr*). m.p. 63.1–63.8 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.38 (d, *J* = 6.96 Hz, 2H), 3.62 (t, *J* = 6.96 Hz, 1H), 3.76 (s, 3H), 3.95 (s, 1H), 5.00–5.07 (m, 2H), 5.65–5.79 (m, 2H), 5.97 (brs, 1H), 6.81 (d, *J* = 8.61 Hz, 2H), 7.03 (brs, 1H), 7.07 (d, *J* = 8.61 Hz, 2H), 7.14–7.26 (m, 3H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 40.22 (t), 54.88 (q), 64.71 (d), 110.72 (d), 117.07 (t), 120.45 (d), 127.17 (d), 127.85 (d), 128.38 (d), 128.62 (d), 129.49 (s), 135.65 (d), 139.43 (s), 157.33 (s), 176.32 (s) ppm. Anal. calcd. for $C_{19}H_{22}N_2O_2 \cdot ½\ H_2O$: C, 71.45 %; H, 7.26 %; N, 8.77 %. Found: C, 71.43 %; H, 6.88 %; N, 8.76 %. MS (CI): *m/z* = 311 [M + H$^+$].



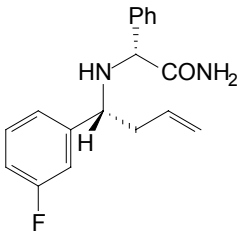
(2*R*)-2-{[(1*R*)-1-(3-methoxyphenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.38): (pale yellow solid, 99 % yield, >99:1 *dr*). m.p. 96.6–97.2 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.08 (brs, 1H), 2.38 (d, *J* = 6.96 Hz, 1H), 3.65 (t, *J* = 6.96 Hz, 1H), 3.73 (s, 3H), 3.97 (s, 1H), 5.02–5.09 (m, 2H), 5.68–5.81 (m, 1H), 5.98 (brs, 1H), 6.70–6.77 (m, 3H), 6.99 (brs, 1H), 7.17–7.26 (m, 6H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.24 (t), 54.81 (q), 61.29 (d), 63.97 (d), 112.35 (d), 112.51 (d), 117.38 (t), 119.05 (d), 126.96 (d), 127.68 (d), 128.44 (d), 129.28 (d), 134.65 (d), 139.17 (s), 144.23 (s), 159.51 (s), 175.70 (s) ppm. Anal. calcd. for $C_{19}H_{22}N_2O_2 \cdot ½\ H_2O$: C, 71.45 %; H, 7.26 %; N, 8.77 %. Found: C, 71.45 %; H, 6.90 %; N, 8.79 %. MS (CI): *m/z* = 311 [M + H$^+$].



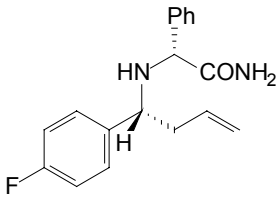
(2*R*)-2-{[(1*R*)-1-(4-methoxyphenyl)-3-butenyl] amino}-2-phenyl ethanamide (3.39): (pale yellow solid, 99 % yield, >99:1 *dr*). m.p. 92.2–92.7 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.38 (d, *J* = 6.96 Hz, 2H), 3.62 (t, *J* = 6.96 Hz, 1H), 3.76 (s, 3H), 3.95 (s, 1H), 5.00–5.07 (m, 2H), 5.65–5.79 (m, 2H), 5.97 (brs, 1H), 6.81 (d, *J* = 8.61 Hz, 2H), 7.03 (brs, 1H), 7.07 (d, *J* = 8.61 Hz, 2H), 7.14–7.26 (m, 3H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.13 (t), 54.96 (q), 60.92 (d), 63.88 (d), 113.69 (t), 117.43 (t), 127.06 (d), 127.82 (d), 127.95 (d), 128.55 (d), 134.00 (s), 134.66 (d), 138.86 (s), 158.62 (s), 175.95 (s) ppm. Anal. calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52 %; H, 7.10 %; N, 9.00 %. Found: C, 73.70 %; H, 6.95 %; N, 9.04 %. MS (CI): *m/z* = 311 [M + H$^+$].



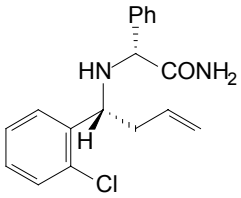
(2*R*)-2-{[(1*R*)-1-(2-fluorophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.40): (pale yellow oil, which became a semi-solid on standing, >99 % yield, 98:2 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.20 (brs, 1H), 2.46 (dt, J = 6.96 Hz, 2H), 3.94 (s, 1H), 3.99 (t, J = 6.96 Hz, 1H), 5.02–5.09 (m, 2H), 5.69–5.83 (m, 1H), 6.95-7.08 (m, 3H), 7.13–7.28 (m, 8H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 40.91 (t), 56.26 (d), 64.63 (d), 115.58 (d, $^{2}J_{C\text{-}F}$ = 21.97 Hz), 117.76 (t), 124.06 (d, $^{4}J_{C\text{-}F}$ = 3.66 Hz), 127.02 (d), 127.91 (d), 128.34 (d, $^{3}J_{C\text{-}F}$ = 4.88 Hz), 128.62 (d), 128.77 (d), 129.20 (s, $^{3}J_{C\text{-}F}$ = 12.20 Hz), 134.57 (d), 139.12 (s), 160.91 (s, $^{1}J_{C\text{-}F}$ = 245.38 Hz), 175.62 (s) ppm. Anal. calcd. for $C_{18}H_{19}FN_2 \cdot ½H_2O$: C, 70.34 %; H, 6.56 %; N, 9.11 %. Found: C, 70.63 %; H, 6.17 %; N, 9.39 %. MS (CI): m/z = 299 [M + H$^+$].



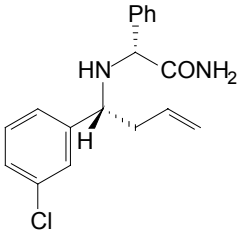
(2*R*)-2-{[(1*R*)-1-(3-fluorophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.41): (yellow oil, which became a semi-solid on standing, 97 % yield, 98:2 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.20 (brs, 1H), 2.37 (d, J = 6.96 Hz, 2H), 3.68 (t, J = 6.96 Hz, 1H), 3.92 (s, 1H), 5.01–5.07 (m, 2H), 5.63–5.76 (m, 1H), 6.71 (brs, 1H), 6.87–6.95 (m, 4H), 7.15–7.26 (m, 6H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.32 (t), 61.12 (d), 64.31 (d), 113.66 (d, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 114.15 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 118.04 (t), 122.70 (d, $^{3}J_{C\text{-}F}$ = 2.4 Hz), 127.09 (d), 128.06 (d), 128.76 (d), 129.98 (d, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 134.36 (d), 139.00 (s), 145.49 (s, $^{3}J_{C\text{-}F}$ = 7.3 Hz), 162.95 (s, $^{1}J_{C\text{-}F}$ = 246.6 Hz), 175.57 (s) ppm. Anal. calcd. for $C_{18}H_{19}FN_2$: C, 72.46 %; H, 6.42 %; N, 9.39 %. Found: C, 72.19 %; H, 6.30 %; N, 9.51 %. MS (CI): m/z = 299 [M + H$^+$].



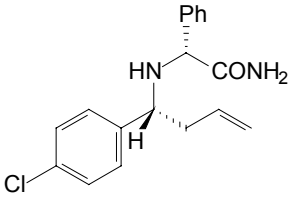
(2*R*)-2-{[(1*R*)-1-(4-fluorophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.42): (yellow oil, which became a semi-solid on standing, 94 % yield, 99:1 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.14 (brs, 2H), 2.35 (t, J = 6.96 Hz, 2H), 3.65 (t, J = 6.95 Hz, 1H), 3.88 (s, 1H), 4.99–5.05 (m, 2H), 5.58–5.69 (m, 1H), 6.44 (brs, 1H), 6.96 (t, J = 8.70 Hz, 2H), 7.08–7.12 (m, 4H), 7.18–7.22 (m, 4H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.32 (t), 61.32 (d), 64.28 (d), 115.45 (d, $^{2}J_{C\text{-}F}$ = 13.8 Hz), 118.17 (t), 127.22 (d), 128.34 (d), 128.68 (d, $^{3}J_{C\text{-}F}$ = 5.7 Hz), 134.29 (d), 137.72 (s), 138.61 (s), 162.07 (s, $^{1}J_{C\text{-}F}$ = 162.7 Hz), 175.72 (s) ppm. MS (CI): m/z = 299 [M + H$^+$].



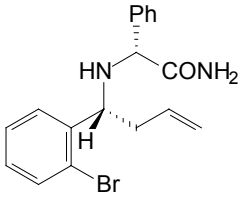
(2*R*)-2-{[(1*R*)-1-(2-chlorophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.43): (pale yellow oil, which crystallizes on standing, 98 % yield, 97:3 *dr*). m.p. 110.4–111.0 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.32–2.52 (m + brs, 3H), 3.89 (s, 1H), 4.25 (t, *J* = 6.78 Hz, 1H), 4.99–5.10 (m, 2H), 5.68–5.82 (m, 1H), 6.55 (brs, 1H), 7.04 (brs, 1H), 7.12–7.30 (m, 9H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 40.72 (t), 58.20 (d), 64.49 (d), 118.12 (t), 126.96 (d), 127.17 (d), 127.70 (d), 128.12 (d), 128.40 (d), 128.79 (d), 129.90 (d), 133.76 (s), 134.40 (d), 138.92 (s), 139.35 (s), 175.64 (s) ppm. Anal. calcd. for $C_{18}H_{19}ClN_2O$: C, 68.67 %; H, 6.08 %; N, 8.90 %. Found: C, 68.51 %; H, 6.29 %; N, 8.75 %. MS (CI): *m/z* = 315 (100.0) [M + H^+], 317 (35.8) [M + H^+].



(2*R*)-2-{[(1*R*)-1-(3-chlorophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.44): (white plates, 83 % yield, 98:2 *dr*). m.p. 39.2–40.3 °C. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.15 (brs, 1H), 2.33 (d, *J* = 6.84 Hz, 2H), 3.63 (t, *J* = 6.84 Hz, 1H), 3.88 (s, 1H), 4.97–5.05 (m, 2H), 5.55–5.75 (m, 1H), 6.54 (brs, 1H), 6.82 (brs, 1H), 6.97–7.24 (m, 8H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.35 (t), 61.26 (d), 64.34 (d), 118.17 (t), 125.22 (d), 127.13 (d), 127.55 (d), 128.15 (d), 128.82 (d), 129.79 (d), 134.21 (d), 134.42 (s), 138.87 (s), 144.77 (s), 175.53 (s) ppm. Anal. calcd. for $C_{18}H_{19}ClN_2O$: C, 68.67 %; H, 6.08 %; N, 8.90 %. Found: C, 68.32 %; H, 6.16 %; N, 8.76 %. MS (CI): *m/z* = 315 (100.0) [M + H^+], 317 (35.0) [M + H^+].

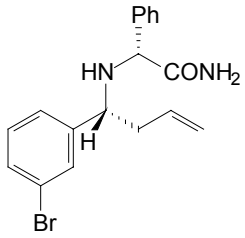


(2*R*)-2-{[(1*R*)-1-(4-chlorophenyl)-3-butenyl] amino}-2-phenyl ethanamide (3.45): (yellow solid, 98 % yield, >99:1 *dr*). m.p. 111.3–112.0 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.33–2.47 (m + brs, 3H), 3.71 (t, *J* = 6.96 Hz, 1H), 3.97 (s, 1H), 5.58–5.72 (m, 2H), 5.99 (brs, 1H), 6.80 (brs, 1H), 7.06–7.13 (m, 4H), 7.21–7.24 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.22 (t), 61.33 (d), 64.30 (d), 118.38 (t), 127.22 (d), 128.41 (d), 128.53 (d), 128.77 (d), 129.00 (d), 133.25 (s), 124.13 (d), 138.45 (s), 140.48 (s), 175.47 (s) ppm. Anal. calcd. for $C_{18}H_{19}ClN_2O$: C, 68.67 %; H, 6.08 %; N, 8.90 %. Found: C, 68.24 %; H, 5.88 %; N, 8.63 %. MS (CI): *m/z* = 315 (100.0) [M + H^+], 317 (35.7) [M + H^+].

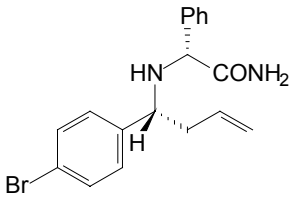


(2*R*)-2-{[(1*R*)-1-(2-bromophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.46): (pale yellow oil, 98 % yield, >99:1 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.24–2.50 (m + brs, 3H), 3.88 (s, 1H), 4.24 (dd, *J* = 8.06, *J* = 5.13 Hz, 1H), 5.05–5.15 (m, 2H), 5.71–5.83 (m, 1H), 6.45 (brs, 1H), 6.99 (brs, 1H), 7.06 (dt, *J* = 7.51, *J* =

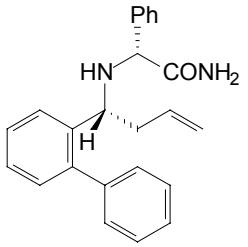
1.83 Hz, 1H), 7.16–7.24 (m, 7H), 7.49 (d, J = 7.69 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 38.64 (t), 57.72 (d), 62.02 (d), 115.72 (d), 121.87 (d), 124.77 (d), 125.17 (t), 125.49 (d), 125.62 (d), 126.27 (d), 126.34 (d), 130.74 (d), 132.08 (d), 136.77 (s), 138.86 (s), 173.11 (s) ppm. MS (CI): *m/z* = 359 (39.8) [M + H$^+$], 361 (39.4) [M + H$^+$].



(2*R*)-2-{[(1*R*)-1-(3-bromophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.47): (pale yellow oil, 99 % yield, >99:1 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.27 (brs, 1H), 2.41 (dt, J = 6.96 Hz, 2H), 3.66 (t, J = 6.96 Hz, 1H), 3.94 (s, 1H), 5.02–5.13 (m, 2H), 5.61–5.74 (m, 1H), 6.26 (brs, 1H), 6.84 (brs, 1H), 7.08–7.30 (m, 8H), 7.33 (dd, J = 7.69, J = 1.1 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.29 (t), 61.35 (d), 64.27 (d), 118.24 (t), 122.69 (s), 124.39 (d), 125.76 (d), 127.17 (d), 128.19 (d), 128.84 (d), 130.08 (d), 130.51 (d), 134.13 (d), 138.71 (s), 144.91 (s), 175.56 (s) ppm. Anal. calcd. for $C_{18}H_{19}BrN_2O$: C, 60.18 %; H, 5.33 %; N, 7.80 %. Found: C, 59.84 %; H, 5.21 %; N, 7.67 %. MS (CI): *m/z* = 359 (100.0) [M + H$^+$], 361 (99.3) [M + H$^+$].



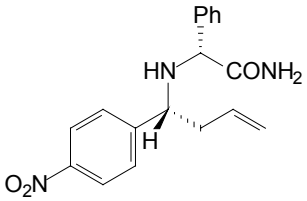
(2*R*)-2-{[(1*R*)-1-(4-bromophenyl)-3-butenyl] amino}-2-phenyl ethanamide (3.48): (white solid, 95 % yield, >99:1 *dr*). m.p. 115.6–116.5 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.24 (brs, 1H), 2.31–2.48 (m, 2H), 3.68 (t, J = 6.78 Hz, 1H), 3.93 (s, 1H), 5.01–5.07 (m, 2H), 5.60–5.73 (m, 1H), 6.30 (brs, 1H), 6.84 (brs, 1H), 7.03 (d, J = 8.24 Hz, 2H), 7.11–7.14 (m, 2H), 7.22–7.24 (m, 3H), 7.39 (d, J = 8.24 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.27 (t), 61.25 (d), 64.31 (d), 118.28 (t), 121.23 (s), 127.19 (d), 128.29 (d), 128.85 (d), 128.93 (d), 131.67 (d), 134.21 (d), 138.69 (s), 141.31 (s), 175.62 (s) ppm. Anal. calcd. for $C_{18}H_{19}BrN_2O$: C, 60.18 %; H, 5.33 %; N, 7.80 %. Found: C, 59.75 %; H, 5.37 %; N, 7.72 %. MS (CI): *m/z* = 359 (100.0) [M + H$^+$], 361 (99.8) [M + H$^+$].



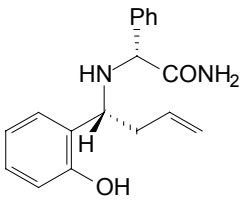
(2*R*)-2-{[(1*R*)-1-[1,1'-biphenyl]-2-yl-3-butenyl]amino}-2-phenyl ethanamide (3.49): (pale yellow solid, 89 % yield, >99:1 *dr*). ^{1}H-NMR (500MHz, $CDCl_3$): δ = 2.16 (brs, 1H), 2.28–2.41 (m, 2H), 3.99 (dt, J = 5.41, J = 2.95 Hz, 1H), 4.01 (s, 1H), 4.99–5.04 (m, 2H), 5.64–5.73 (m, 1H), 5.78 (brs, 1H), 7.04 (brs, 1H), 7.23–7.25 (m, 5H), 7.29–7.41 (m, 9H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.22 (t), 56.89 (d), 64.64 (d), 125.26 (d), 126.73 (d), 127.03 (d), 127.17 (d), 127.79 (t), 128.00 (d), 128.08 (d), 128.74 (d), 129.23 (d), 130.07 (d), 134.96 (d), 139.44 (s), 140.18 (s), 140.68 (s), 142.53 (s), 175.25 (s) ppm. MS (CI): *m/z* = 357 [M + H$^+$].

6.57 (brs, 1H), 7.15–7.27 (m, 5H), 7.42–7.57 (m, 2H), 8.06–8.11 (m, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.32 (t), 61.42 (d), 64.72(d), 118.96 (t), 122.07 (d), 122.52 (d), 127.32 (d), 128.46 (d), 129.01 (d), 129.46 (d), 133.42 (d), 133.58 (d), 138.29 (s), 144.75 (s), 148.37 (s), 174.96 (s) ppm. Anal. calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45 %; H, 5.89 %; N, 12.91 %. Found: C, 66.21 %; H, 5.80 %; N, 12.82 %. MS (CI): *m/z* =326 [M + H^+].

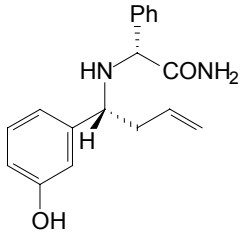
(2*R*)-2-{[(1*R*)-1-(4-nitrophenyl)-3-butenyl] amino}-2-phenyl ethanamide (3.54): (orange oil, 93 % yield, 99:1 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.38–2.47 (m, 1H), 2.54–2.63 (m, 1H), 2.75 (brs, 1H), 3.93 (t, *J* = 6.23 Hz, 1H), 4.07 (s, 1H), 4.97–5.02 (m, 2H), 5.49–5.63 (m, 1H), 6.58 (brs, 1H), 6.77 (brs, 1H), 7.07–7.18 (m, 5H), 7.29 (d, *J* = 8.61 Hz, 2H), 8.03 (d, *J* = 8.61 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 41.77 (t), 61.71 (d), 64.28 (d), 119.09 (t), 123.72 (d), 124.26 (d), 127.40 (d), 128.75 (d), 129.14 (d), 133.01 (d), 137.43 (s), 147.28 (s), 149.05 (s), 176.29 (s) ppm. Anal. calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45 %; H, 5.89 %; N, 12.91 %. Found: C, 66.32 %; H, 5.90 %; N, 12.88 %. MS (CI): *m/z* = 326 [M + H^+].



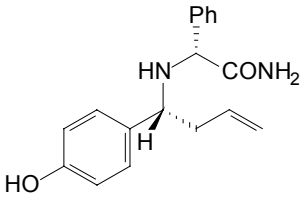
(2*R*)-2-{[(1*R*)-1-(2-hydroxyphenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.55): (yellow oil which crystallizes on standing, 95 % yield, >99:1 *dr*). m.p. 174.6–175.9 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.44 (dt, *J* = 6.95 Hz, 2H), 3.78 (t, *J* = 6.96 Hz, 1H), 4.12 (s, 1H), 5.06–5.10 (m, 2H), 5.66 (brs, 1H), 5.71–5.85 (m, 1H), 5.87 (brs, 1H), 6.74 (d, *J* = 6.96 Hz, 2H), 6.90 (d, *J* = 7.69 Hz, 1H), 7.09 (t, *J* = 7.69 Hz, 1H), 7.17–7.24 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 40.51 (t), 61.61 (d), 62.73 (d), 116.89 (t), 118.80 (t), 119.21 (d), 124.61 (s), 127.33 (d), 128.37 (d), 128.71 (d), 128.90 (d), 129.08 (d), 134.08 (d), 137.50 (s), 150.91 (d), 156.87 (s), 173.33 (s) ppm. Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.95 %; H, 6.80 %; N, 9.45 %. Found: C, 73.03 %; H, 6.71 %; N, 9.47 %. MS (CI): *m/z* = 297 [M + H^+].



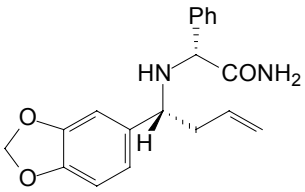
(2*R*)-2-{[(1*R*)-1-(3-hydroxyphenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.56): (yellowish oil which crystallizes on standing, 97 % yield, >99:1 *dr*). m.p. 178.7–179.4 °C. ^{1}H-NMR (300MHz, $CDCl_3$/ [D_6]DMSO): δ = 1.81 (d, *J* = 6.59 Hz, 1H), 1.99 (brs, 2H), 3.03 (t, *J* = 6.59 Hz, 1H), 3.42 (s, 1H), 4.43–4.52 (m, 2H), 5.10–5.24 (m, 1H), 6.14 (brs, 1H), 6.36 (d, 1H), 6.40 (d, 2H), 6.53 (t, *J* = 7.69 Hz, 1H), 6.90–6.94 (m, 5H), 7.02 (brs, 1H), 8.55 (brs, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 41.27 (t), 58.89 (d), 61.24 (d), 112.46 (d), 115.41 (t), 116.31 (d), 125.39 (d), 125.49 (d), 126.46 (d), 127.48 (d), 133.84 (d), 138.68 (s), 143.42 (s), 155.80 (s), 173.00 (s)



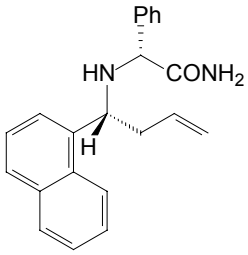
ppm. Anal. calcd for $C_{18}H_{20}N_2O_2 \cdot H_2O$: C, 68.77 %; H, 7.05 %; N, 8.91 %. Found: C, 69.57 %; H, 6.51 %; N, 9.64 %. MS (CI): *m/z* = 297 [M + H^+].



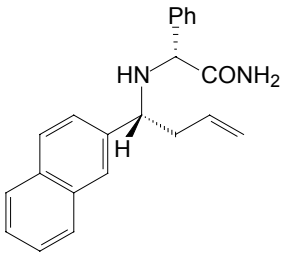
(2*R*)-2-{[(1*R*)-1-(4-hydroxyphenyl)-3-butenyl] amino}-2-phenyl ethanamide (3.57): (colorless solid, 97 % yield, 99:1 *dr*). m.p. 158.0–159.0 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 2.21 (dt, *J* = 6.96 Hz, 2H), 3.42 (t, *J* = 6.96 Hz, 1H), 3.81 (s, 1H), 4.83–4.90 (m, 2H), 5.50–5.61 (m, 1H), 6.01 (brs, 1H), 6.60 (d, *J* = 8.43 Hz, 2H), 6.86 (d, *J* = 8.43 Hz, 2H), 7.05–7.21 (m + brs, 6H), 8.55 (brs, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 41.20 (t), 59.12 (d), 62.12 (d), 113.78 (d), 115.62 (t), 125.54 (d), 126.02 (d), 126.47 (d), 126.90 (d), 131.77 (s), 133.80 (d), 138.24 (s), 154.82 (s), 173.69 (s) ppm. Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.95 %; H, 6.80 %; N, 9.45 %. Found: C, 72.90 %; H, 6.84 %; N, 9.45 %. MS (CI): *m/z* = 297 [M + H^+].



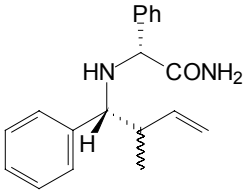
(2*R*)-2-{[(1*R*)-1-(1,3-benzodioxol-5-yl)-4-pentenyl] amino}-2-phenyl ethanamide (3.58): (colorless crystals, 81 % yield, >99:1 *dr*) m.p. 110.0–111.0 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.34–2.39 (dd, *J* = 6.96 Hz, 2H), 3.60 (t, *J* = 6.96 Hz, 1H), 3.99 (s, 1H), 5.00–5.07 (m, 2H), 5.64–5.74 (m, 2H), 5.90 (s, 2H), 6.61–6.72 (m, 3H), 6.93 (brs, 1H), 7.21–7.23 (m, 5H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 41.12 (t), 59.92 (d), 69.92 (d), 99.51 (t), 105.47 (d), 106.64 (d), 116.25 (d), 119.03 (t), 125.72 (d), 126.56 (d), 127.31 (d), 133.47 (s), 135.21 (d), 137.87 (s), 145.30 (s), 146.46 (s), 174.24 (s) ppm. Anal. calcd for $C_{19}H_{20}N_2O_3$: C, 70.35 %; H, 6.21 %; N, 8.64 %. Found: C, 70.28 %; H, 6.33 %; N, 8.59 %. MS (CI): *m/z* = 325 [M + H^+].



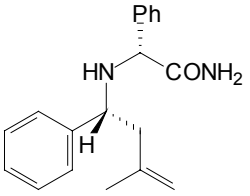
(2*R*)-2-{[(1*R*)-1-(1-naphthyl)-3-butenyl]amino}-2-phenyl ethanamide (3.59): (pale yellow solid, which was recrystallized from acetone/hexane, 95 % yield, >99:1 *dr*) m.p. 103.0–103.8 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 2.41–2.51 (m + brs, 2H), 2.59–2.67 (m, 1H), 3.99 (s, 1H), 4.64 (dt, *J* = 7.69, *J* = 5.13 Hz, 1H), 5.05–5.15 (m, 2H), 5.75–5.89 (m, 1H), 6.34 (brs, 1H), 6.96 (brs, 1H), 7.21-7.24 (m, 5H), 7.35-7.50 (m, 4H), 7.74 (d, *J* = 7.32 Hz, 1H), 7.85 (d, *J* = 7.69 Hz, 1H), 8.11 (d, *J* = 7.32 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 41.69 (t), 63.93 (d), 117.64 (t), 122.43 (d), 122.82 (d), 125.02 (d), 125.28 (d), 125.83 (d), 126.93 (d), 127.43 (d), 127.67 (d), 128.43 (d), 128.66 (d), 131.31 (s), 133.63 (s), 134.63 (d), 137.97 (s), 139.03 (s), 175.77 (s) ppm. Anal. calcd for $C_{22}H_{22}N_2O$: C, 79.97 %; H, 6.71 %; N, 8.48 %. Found: C, 79.72 %; H, 6.76 %; N, 8.58 %. MS (CI): *m/z* = 331 [M+1].



(2*R*)-2-{[(1*R*)-1-(2-naphthyl)-4-pentenyl]amino}-2-phenyl ethanamide (3.60): (pale yellow solid, which was recrystallized from acetone/hexane, 73 % yield, >99:1 *dr*) m.p. 105.8–108.0 °C. ^{1}H-NMR (300MHz, $CDCl_3$-/[D_6]DMSO): δ = 2.45 (brs, 1H), 2.49 (t, J = 6.78 Hz, 2H), 3.86 (t, J = 6.78 Hz, 1H), 3.99 (s, 1H), 5.03–5.12 (m, 2H), 5.71–5.84 (m, 1H), 6.43 (brs, 1H), 6.99 (brs, 1H), 7.16–7.23 (m, 5H), 7.31 (d, J = 8.42 Hz, 1H), 7.41–7.48 (m, 2H), 7.63 (s, 1H), 7.75–7.81 (m, 3H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.24 (t), 61.45 (d), 64.07 (d), 117.61 (t), 124.32 (d), 125.59 (d), 125.99 (d), 126.10 (d), 127.03 (d), 127.43 (d), 127.58 (d), 127.75 (d), 128.30 (d), 128.53 (d), 132.67 (s), 133.01 (s), 134.71 (d), 139.20 (s), 139.86 (s), 175.74 (s) ppm. Anal. calcd for $C_{22}H_{22}N_2O$: C, 79.97 %; H, 6.71 %; N, 8.48 %. Found: C, 80.08 %; H, 6.75 %; N, 8.35 %. MS (CI): m/z = 331 [M+1].



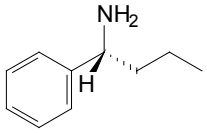
2-{[2-methyl-1-phenyl-3-butenyl]amino}-2-phenyl ethanamide (3.61): A solution of crotylzinc bromide (1.5 equiv.) was prepared by adding crotylbromide (62.6 mmol, 6.4 mL) to finely cut zinc-wool (62.6 mmol, 4.0 g) in THF (50 mL). The solution of crotylzinc bromide was cooled to room temperature and was added dropwise to a solution of **3.2** (41.7 mmol, 10.0 gram) in THF (30 mL) at 0^{o}C. Workup was performed as described above. Evaporation of the solvent provided a mixture of isomers ((*R*,*R*,*R*):(*R*,*R*,*S*)=1:1.3). (orange oil, 98 % yield). ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.78 (d, J = 6.59 Hz, 3H), 0.92 (d, J = 6.95 Hz, 3H), 2.31–2.41 (m, 1H), 2.41–2.65 (m, 1H), 3.36 (d, J = 8.42 Hz, 1H), 3.70 (d, J = 5.13 Hz, 1H), 3.89 (s, 1H), 3.97 (s, 1H), 4.46–5.58 (m, 1H), 4.98–5.15 (m, 2 × 2H), 5.72–5.84 (m, 1H), 6.44 (brs, 1H), 6.69 (brs, 1H), 6.99–7.29 (m, 2 × 10H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 15.0 (q), 16.3 (q), 42.2 (d), 43.2 (d), 62.5 (d), 62.6 (d), 64.9 (d), 65.3 (d), 114.6 (t), 115.3 (t), 125.8 (d), 126.1 (d), 126.2 (d), 126.3 (d), 126.7 (d), 126.7 (d), 126.8 (d), 127.0 (d), 127.3 (d), 127.6 (d), 136.9 (s), 137.5 (d), 138.0 (d), 139.7 (s), 139.9 (s), 175.2 (s), 175.5 (s) ppm.



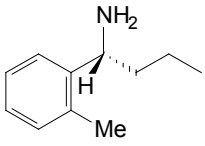
(2*R*)-2-{[(1*R*)-3-methyl-1-phenyl-3-butenyl]amino}-2-phenyl ethanamide (3.62): A solution of methallylzinc bromide (1.5 equiv.) was prepared by adding methallylbromide (62.6 mmol, 6.30 mL) to finely cut zinc-wool (4.0 gram, 62.6 mmol) in THF (50 mL). The solution of methallylzinc bromide was cooled to room temperature and was added dropwise to a solution of **3.2** (10 gram, 41.7 mmol) in THF (30 mL) at 0 ^{o}C. The reaction mixture was warmed to room temperature and was poured into water (100 mL). Ethylacetate (30 mL) was added and the mixture was stirred vigorously. After filtration through a glass filter, the organic phase was separated and the water layer was extracted

with ethylacetate (2 x 30 mL). The combined organic phase was dried on magnesium sulphate and the ethylacetate was evaporated furnishing **31** that can be crystallized from diethylether (colorless solid, 98 % yield). m.p. 104.0–109.0 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.72 (s, 3H), 2.27–2.43 (m, 2H), 3.75–3.80 (m, 1H), 4.00 (s, 1H), 4.73 (s, 1H), 4.80 (s, 1H), 5.76 (brs, 1H), 6.95 (brs, 1H), 7.14–7.30 (m, 10H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 21.1 (q), 44.9 (t), 62.5 (d), 63.7 (d), 112.4 (t), 125.7 (d), 125.9 (d), 126.2 (d), 126.8 (d), 127.2 (d), 127.4 (d), 136.9 (d), 140.5 (s), 140.7 (s), 175.1 (s) ppm.

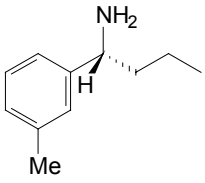
Typical Procedure for the Catalytic Hydrogenation of (*R*)-PGA Homoallylamines 3.24–3.33 and 3.40. The PGA homoallylamine (15.0 mmol) was dissolved in *i*-propanol (75 mL). Water (75 mL), acetic acid (100 mL), and Pd–C (10 %) (0.6 gram, cat.) were added successively. After two vacuum/H_2 cycles to remove air from the reaction flask, the stirred mixture of the substrate was hydrogenated at ambient pressure of H_2 at room temperature for 5 days. After filtration, the *i*-propanol was evaporated under reduced pressure. The residue was diluted with water (50 mL) and while acidic, the reaction mixture was washed once with diethyl ether to remove any by-products. The aqueous phase was brought to pH 10 with 10 % NaOH and was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine and dried over sodium sulphate. After evaporation of the dichloromethane, pentane was added to the residue. Filtration through a glass filter yielded crystalline phenyl acetamide as the by-product. Evaporation of the pentane of the filtrate yielded the primary substituted *(R)*-arylbutylamine as an oil.



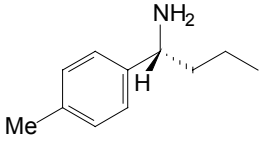
(1*R*)-1-phenylbutylamine (3.64): (colorless oil which crystallizes into white needless on standing, 70 % yield). $[\alpha]_D^{27}$ = +18.3 (*c* = 1.06, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.86 (t, 3H, *J* = 7.32 Hz), 1.14–1.37 (m, 2H), 1.58 (brs, 2H), 1.50–1.77 (m, 2H), 3.84 (t, *J* = 6.96 Hz, 1H), 7.17–7.31 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 13.87 (q), 19.58 (t), 41.72 (t), 55.84 (d), 126.14 (d), 126.64 (d), 128.22 (d), 146.67 (s) ppm. Anal. calcd for $C_{10}H_{15}N$: C, 80.48 %; H, 10.13 %; N, 9.39 %. Found: C, 79.95 %; H, 10.01 %; N, 9.21 %. MS (CI): *m/z* = 150 [M + H^+].



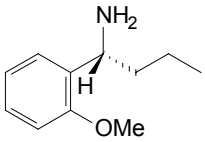
(1*R*)-1-(2-methylphenyl)butylamine (3.65): (yellow oil, 95 % yield). $[\alpha]_D^{25}$ = +32.8 (c = 2.08, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.33 Hz, 3H), 1.20–1.44 (m, 2H), 1.52 (brs, 2H), 1.46–1.63 (m, 2H), 2.31 (s, 3H), 4.14 (t, *J* = 6.59 Hz, 1H), 7.09 (dd, *J* = 4.39 Hz, 2H), 7.14–7.22 (m, 1H), 7.37 (d, *J* = 7.33 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.81 (q), 19.55 (t), 21.21 (q), 41.58 (t), 55.73 (d), 123.12 (d), 126.76 (d), 127.31 (d), 128.03 (d), 137.67 (s), 146.53 (s) ppm. Anal. calcd. for $C_{11}H_{17}N$: C, 80.93 %; H, 10.50 %; N, 8.58 %. Found: C, 80.69 %; H, 10.62 %; N, 8.46 %. MS (CI): *m/z* = 164 [M + H^+].



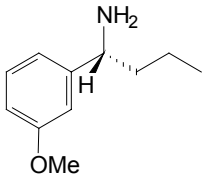
(1*R*)-1-(3-methylphenyl)butylamine (3.66): (yellow oil, 92 % yield). $[\alpha]_D^{25}$ = +13.59 (c = 1.13, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.33 Hz, 3H), 1.18–1.38 (m, 2H), 1.44 (brs, 2H), 1.56–1.64 (m, 2H), 2.31 (s, 3H), 3.80 (t, *J* = 6.96 Hz, 1H), 7.00 (d, *J* = 7.51 Hz, 1H), 7.05 (d, *J* = 7.51 Hz, 1H), 7.09 (s, 1H), 7.17 (t, *J* = 7.51 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.79 (q), 19.53 (t), 21.19 (q), 41.60 (t), 55.71 (d), 123.10 (d), 126.73 (d), 127.25 (d), 127.99 (d), 137.61 (s), 146.55 (s) ppm. MS (CI): *m/z* = 164 [M + H$^+$].



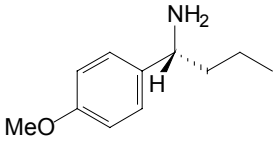
(1*R*)-1-(4-methylphenyl)butylamine (3.67): (yellow oil, which crystallizes on standing, 91 % yield). m.p. 55.0–56.5 °C. $[\alpha]_D^{25}$ = +19.34 (c = 2.23, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.32 Hz, 3H), 1.13–1.34 (m, 2H), 1.70 (brs, 2H), 1.75–1.50 (m, 2H), 2.26 (s, 3H), 3.77 (t, *J* = 6.96 Hz, 1H), 7.06 (d, *J* = 8.06 Hz, 2H), 7.13 (d, *J* = 8.06 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.56 (q), 19.27 (t), 20.50 (q), 41.35 (t), 55.19 (d), 125.73 (d), 128.55 (d), 135.68 (s), 143.24 (s) ppm. MS (CI): *m/z* = 164 [M + H$^+$].



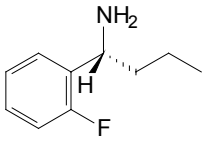
(1*R*)-1-(2-methoxyphenyl)butylamine (3.68): (colorless oil, which crystallizes on standing, 87 % yield). m.p. 56.8–57.6 °C. $[\alpha]_D^{25}$ = +4.49 (c = 3.45, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.32 Hz, 3H), 1.15–1.39 (m, 2H), 1.53–1.90 (m + brs, 3H), 3.76 (s, 3H), 4.10 (t, *J* = 6.95 Hz, 1H), 6.80 (d, *J* = 8.06 Hz, 1H), 6.87 (t, *J* = 7.33 Hz, 1H), 7.15 (dt, *J* = 8.06, *J* = 1.83 Hz, 1H), 7.21 (dd, *J* = 7.33, *J* = 1.83 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.98 (q), 19.87 (t), 39.66 (t), 50.49 (d), 55.07 (q), 110.39 (d), 120.47 (d), 126.59 (d), 127.36 (d), 134.71 (s), 156.75 (s) ppm. Anal. calcd for $C_{11}H_{17}NO$: C, 73.70 %; H, 9.56 %; N, 7.81 %. Found: C, 73.40 %; H, 9.96 %; N, 7.54 %. MS (CI): *m/z* = 180 [M + H$^+$].



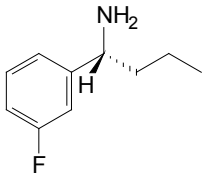
(1*R*)-1-(3-methoxyphenyl)butylamine (3.69): (pale yellow oil, 89 % yield). $[\alpha]_D^{25}$ = +16.4 (c = 3.68, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.32 Hz, 3H), 1.12–1.29 (m, 2H), 1.39 (brs, 2H), 1.49–1.56 (m, 2H), 3.68 (s, 3H), 3.74 (t, *J* = 6.96 Hz, 1H), 6.66 (dd, *J* = 8.06, *J* = 1.84 Hz, 1H), 6.77–6.79 (m, 2H), 7.12 (t, *J* = 8.06 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.70 (q), 19.38 (t), 41.49 (t), 54.72 (d), 55.67 (q), 111.61 (d), 111.69 (d), 118.33 (d), 128.99 (d), 148.33 (s), 159.37 (s) ppm. Anal. calcd. for $C_{11}H_{17}NO$: C, 73.70 %; H, 9.56 %; N, 7.81 %. Found: C, 73.59 %; H, 9.54 %; N, 7.81 %. MS (CI): *m/z* = 180 [M + H$^+$].



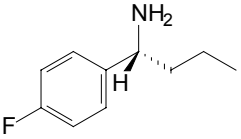
(1*R*)-1-(4-methoxyphenyl)butylamine (3.70): (yellow oil, 89 % yield). $[\alpha]_D^{25}$ = +12.57 (c = 7.39, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.87 (t, J = 7.08 Hz, 3H), 1.14–1.36 (m, 2H), 1.44 (brs, 2H), 1.50–1.69 (m, 2H), 3.76 (s, 3H), 3.82 (t, J = 6.84 Hz, 1H), 6.84 (d, J = 8.79 Hz, 2H), 7.20 (d, J = 8.79 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.86 (q), 19.60 (t), 41.77 (t), 55.01 (q), 55.18 (d), 113.53 (d), 127.14 (d), 138.78 (s), 158.25 (s) ppm. Anal. calcd. for $C_{11}H_{17}NO$: C, 73.70 %; H, 9.56 %; N, 7.81 %. Found: C, 73.58 %; H, 9.47 %; N, 7.67 %. MS (CI): *m/z* = 180 [M + H^+].



(1*R*)-1-(2-fluorophenyl)butylamine (3.71): (pale yellow oil, 58 % yield). $[\alpha]_D^{27}$ = +9.39 (c = 3.21, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.82 (t, J = 7.32 Hz, 3H), 1.11–1.36 (m, 2H), 1.45 (brs, 2H), 1.56–1.63 (m, 2H), 4.10 (t, J = 6.96 Hz, 1H), 6.87–6.93 (m, 1H), 7.04 (dt, J = 7.32, J = 1.10 Hz, 1H), 6.98–7.13 (m, 1H), 7.27 (dt, J = 7.32, J = 1.83 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.72 (q), 19.47 (t), 40.35 (t), 49.49 (d), 115.14 (d, $^2J_{C\text{-}F}$ = 23.20 Hz), 123.94 (d, $^4J_{C\text{-}F}$ = 3.66 Hz), 127.30 (d, $^3J_{C\text{-}F}$ = 4.89 Hz), 127.78 (d, $^3J_{C\text{-}F}$ = 8.45 Hz), 133.39 (s, $^2J_{C\text{-}F}$ = 14.65 Hz), 160.27 (s, $^1J_{C\text{-}F}$ = 294.16 Hz) ppm. MS (CI): *m/z* = 168 [M + H^+].

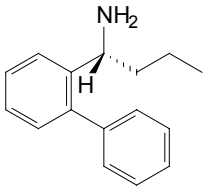


(1*R*)-1-(3-fluorophenyl)butylamine (3.72): (pale yellow oil, 79 % yield). $[\alpha]_D^{25}$ = +16.6 (c = 7.21, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.80 (t, J = 7.03 Hz, 3H), 1.06–1.32 (m, 2H), 1.41 (brs, 2H), 1.44–1.57 (m, 2H), 3.77 (t, J = 6.96 Hz, 1H), 6.79 (dt, J = 8.06 Hz, 1H), 6.95 (dt, J = 8.32 Hz, 2H), 7.15 (dd, J = 13.92, J = 8.06 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 11.40 (q), 17.03 (t), 39.24 (t), 53.06 (d), 110.56 (d, $^2J_{C\text{-}F}$ = 21.97 Hz), 110.99 (d, $^2J_{C\text{-}F}$ = 21.97 Hz), 119.46 (d, $^3J_{C\text{-}F}$ = 2.44 Hz), 127.21 (d, $^4J_{C\text{-}F}$ = 7.33 Hz), 147.11 (s, $^3J_{C\text{-}F}$ = 6.10 Hz), 160.46 (s, $^1J_{C\text{-}F}$ =245.38 Hz) ppm. MS (CI): *m/z* = 168 [M + H^+].

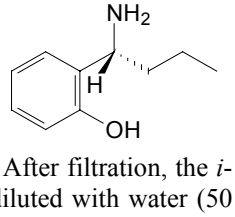


(1*R*)-1-(4-fluorophenyl)butylamine (3.73): (pale yellow oil, 70 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.83 (t, J = 7.33 Hz, 3H), 1.08–1.32 (m, 2H), 1.50 (brs, 2H), 1.45–1.61 (m, 2H), 3.81 (t, J = 6.96 Hz, 1H), 6.92 (dd, J = 8.79, $^2J_{H\text{-}F}$ =8.42 Hz, 2H), 7.20 (dd, J = 5.49, $^3J_{H\text{-}F}$ =8.42 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.76 (q), 19.45 (t), 41.73 (t), 55.12 (d), 114.86 (d, $^2J_{C\text{-}F}$ = 20.98 Hz), 127.61 (d, $^3J_{C\text{-}F}$ =7.63 Hz), 142.20 (s, $^4J_{C\text{-}F}$ = 3.60 Hz), 161.51 (s, $^1J_{C\text{-}F}$ = 244.53 Hz) ppm. MS (CI): *m/z* = 168 [M + H^+].

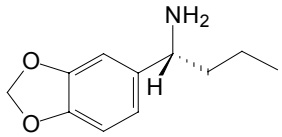
(1*R*)-1-[1,1'-biphenyl]-2-ylbutylamine (3.74): (yellow oil, 87 % yield). $[\alpha]_D^{25}$ = +16.17 (c = 2.18, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.32 Hz, 3H), 0.98–1.28 (m, 2H), 1.47 (brs, 2H), 1.52–1.63 (m, 2H), 4.00 (t, *J* = 6.95 Hz, 1H), 7.16 (d, *J* = 7.69 Hz, 1H), 7.20–7.33 (m, 5H), 7.36 (d, *J* = 6.96 Hz, 2H), 7.52 (d, *J* = 7.69 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.80 (q), 19.63 (t), 41.49 (t), 50.69 (d), 125.47 (d), 126.15 (d), 126.77 (d), 127.80 (d), 127.93 (d), 129.24 (d), 129.79 (d), 141.21 (s), 141.38 (s), 144.07 (s) ppm. MS (CI): *m/z* = 226 [M + H$^+$].



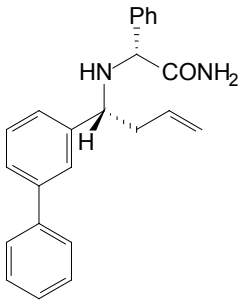
(1*R*)-1-(2-phenol)butylamine (3.79): The *ortho*-bromo-substituted PGA allylamine **3.46** (15.0 mmol) was dissolved in *i*-propanol (75 mL). Water (75 mL), acetic acid (100 mL), and Pd-C (10 %) (0.6 gram, cat.) were added successively. After two vacuum/H_2 cycles to remove air from the reaction flask, the mixture was hydrogenated at ambient pressure of H_2 and room temperature and stirred for 7 days. After filtration, the *i*-propanol was evaporated under reduced pressure. The residue was diluted with water (50 mL) and carefully adjusted to pH 7. The reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phase was washed with brine, dried over sodium sulphate and filtered. After evaporation of the dichloromethane, pentane was added to the residue. Filtration through a glass filter yielded crystalline phenyl acetamide. Evaporation of the pentane of the filtrate yields **3.79** as a colorless oil, which solidifies on standing (83 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.33 Hz, 3H), 1.08–1.49 (m, 3H), 1.52–1.79 (m, 2H), 4.05 (t, *J* = 6.96 Hz, 1H), 6.70 (t, *J* = 7.33 Hz, 1H), 5.68 (d, *J* = 7.33 Hz, 1H), 6.86 (d, *J* = 7.33 Hz), 7.08 (dt, *J* = 7.33, *J* = 1.46 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.86 (q), 19.48 (t), 38.90 (t), 56.54 (d), 117.17 (d), 118.71 (d), 127.13 (s), 128.08 (d), 128.36 (d), 157.60 (s) ppm. Anal. calcd. for $C_{10}H_{15}NO{\cdot}\frac{1}{2}H_2O$: C, 68.93 %; H, 9.26 %; N, 8.04 %. Found: C, 68.85 %; H, 9.35 %; N, 7.90 %. MS (CI): *m/z* = 166 [M + H$^+$].



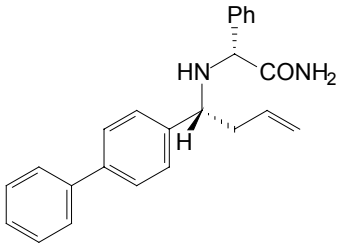
(1*R*)-1-(1,3-benzodioxol-5-yl)butylamine (3.82): (colorless oil, 88 % yield). $[\alpha]_D^{25}$ = +10.9 (c = 1.01, $CHCl_3$). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3H), 1.18–1.26 (m, 2H), 1.58–1.63 (m, 2H), 3.80 (brs, 1H), 5.92 (s, 2H), 6.74 (s, 2H), 6.83 (s, 1H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.44 (q), 18.15 (t), 40.30 (t), 54.22 (d), 99.22 (t), 105.00 (d), 106.32 (d), 117.85 (d), 139.35, 144.67 (s), 146.08 (s) ppm. MS (CI): *m/z* = 194 [M + H$^+$].



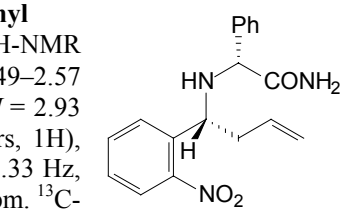
(2*R*)-2-{[(1*R*)-1-[1,1'-biphenyl]-3-yl-3-butenyl]amino}-2-phenyl ethanamide (3.50): (yellow oil, 85 % yield, >99:1 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.37 (brs, 1H), 2.50 (t, J = 6.55 Hz, 2H), 3.83 (t, J = 6.55 Hz, 1H), 4.08 (s, 1H), 5.03–5.16 (m, 2H), 5.74–5.87 (m, 1H), 7.00 (brs, 1H), 7.08 (brs, 1H), 7.19–7.24 (m, 6H), 7.33–7.45 (m, 5H), 7.51 (d, J = 7.69 Hz, 1H), 7.57 (dd, J = 7.69, J = 1.10 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.34 (t), 61.61 (d), 64.17 (d), 117.72 (t), 125.65 (d), 125.80 (d), 126.02 (d), 126.91 (d), 127.09 (d), 127.17 (d), 127.85 (d), 128.53 (d), 128.60 (d), 128.81 (d), 134.63 (d), 139.05 (s), 140.64 (s), 141.22 (s), 142.97 (s), 175.88 (s) ppm. MS (CI): *m/z* = 357 [M + H$^+$].



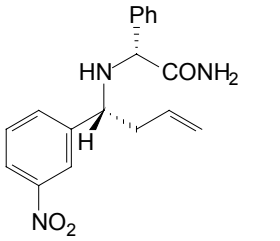
(2*R*)-2-{[(1*R*)-1-[1,1'-biphenyl]-4-yl-3-butenyl] amino}-2-phenylethanamide (3.51): (pale green oil, 99 % yield, >99:1 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.27 (brs, 1H), 2.45 (t, J = 6.59 Hz, 2H), 3.75 (t, J = 6.59 Hz, 1H), 4.02 (s, 1H), 5.04–5.84 (m, 2H), 5.73–5.84 (m, 1H), 6.75 (brs, 1H), 7.04 (brs, 1H), 7.22–7.33 (m, 8H), 7.40 (t, J = 7.32 Hz, 2H), 7.52 (d, J = 8.06 Hz, 2H), 7.56 (d, J = 7.32 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.37 (t), 61.21 (d), 64.52 (d), 117.70 (t), 126.83 (d), 127.11 (d), 127.35 (d), 127.92 (d), 128.64 (d), 134.71 (d), 139.15 (s), 140.12 (s), 140.52 (s), 141.53 (s), 175.72 (s) ppm. MS (CI): *m/z* = 357 [M + H$^+$].



(2*R*)-2-{[(1*R*)-1-(2-nitrophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.52): (orange oil, >99 % yield, >99:1 *dr*). ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 2.35–2.45 (m, 1H), 2.49–2.57 (m, 1H), 2.96 (brs, 1H), 3.93 (s, 1H), 4.35 (dd, J = 5.12, J = 2.93 Hz, 1H), 5.06–5.12 (m, 2H), 5.75–5.89 (m, 1H), 7.00 (brs, 1H), 7.19–7.28 (m + brs, 5H), 7.39–7.44 (m, 2H), 7.60 (t, J = 7.33 Hz, 1H), 7.78 (d, J = 8.06 Hz, 1H), 7.86 (d, J = 7.33 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 41.98 (t), 54.94 (d), 63.10 (d), 117.78 (t), 123.69 (d), 126.94 (d), 127.19 (d), 128.09 (d), 128.84 (d), 133.01 (d), 134.71 (d), 137.90 (s), 139.96 (s), 149.93 (s), 173.75 (s) ppm. Anal. calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45 %; H, 5.89 %; N, 12.91 %. Found: C, 66.06 %; H, 5.97 %; N, 12.72 %. MS (CI): *m/z* = 326 [M + H$^+$].



(2*R*)-2-{[(1*R*)-1-(3-nitrophenyl)-3-butenyl]amino}-2-phenyl ethanamide (3.53): (orange oil, which became a semi-solid on standing, 96 % yield, >99:1 *dr*). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.46–2.62 (m + brs, 3H), 3.92 (t, J = 6.84 Hz, 1H), 4.09 (s, 1H), 5.06–5.13 (m, 2H), 5.61–5.82 (m, 1H), 6.02 (brs, 1H),



3.7 References

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[25] In all cases the addition of 1.5 equiv. of *pre-formed* allylmagnesium bromide to a solution of the imine in THF at ambient temperature failed to produce the adducts.

[26] Crotyl bromide was used consisting of a *cis*/*trans* (1:13) mixture (85 %) and 3-bromo-1-butene (15 %).

[27] X-ray data for **3.57** is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.; fax: (internat.) + 44-1223/336-033; Email: deposit@ccdc.cam.ac.uk, and was allocated the deposition number CCDC 154389.

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Chapter 4
Non-reductive Removal of the (*R*)-Phenylglycine Amide Chiral Auxiliary

In this chapter the syntheses of enantiopure (R)-1-aryl-3-butenylamines and (R)-1-aryl-1-butylamines are described. The unsaturated 1-aryl-3-butenylamines can be synthesized via a non-reductive removal of the PGA chiral auxiliary from the PGA homoallylamines described in Chapter 3. This method provides a broad range of chiral 1-aryl-3-butenylamines in high enantiomeric purity, which can be valuable synthons in the preparation of biologically active compounds or can be used in Dutch Resolution experiments. The saturated (R)-1-aryl-1-butylamines can be obtained by a mild reduction of the free homoallylamines.

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4.1 Introduction

Enantiomerically pure homoallylamines are valuable synthons for the preparation of biologically active compounds such as β-amino acids or esters, 1,3-amino alcohols, and 1-amino-3,4-epoxides as illustrated in Figure 4.1.[1,2] For instance, the application of non-proteinogenic β-amino acids is of topical interest in the synthesis of β-lactam antibiotics.[1c,1d]

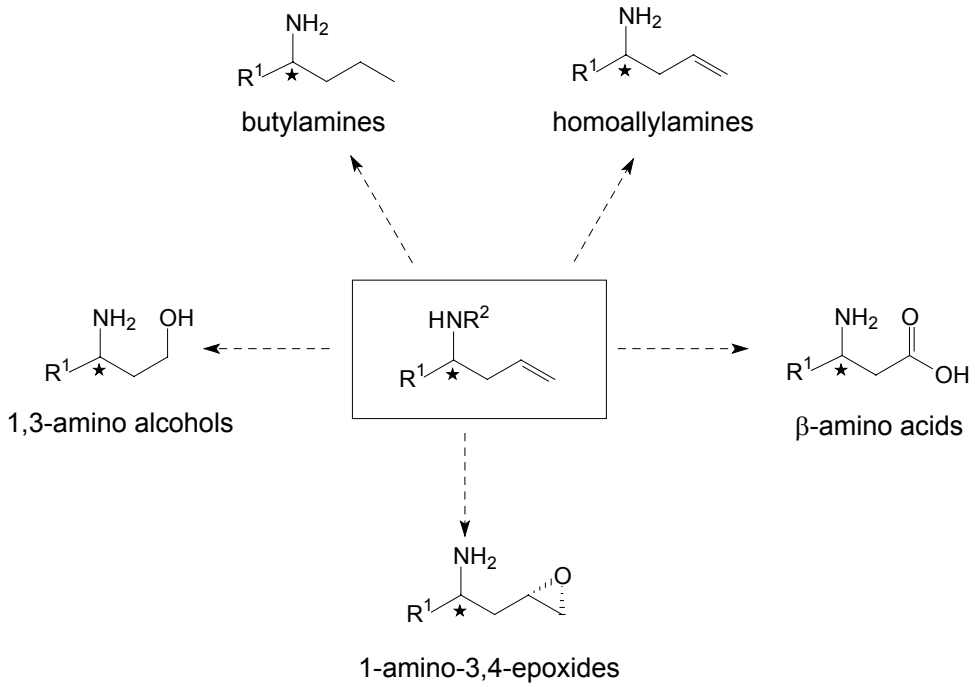
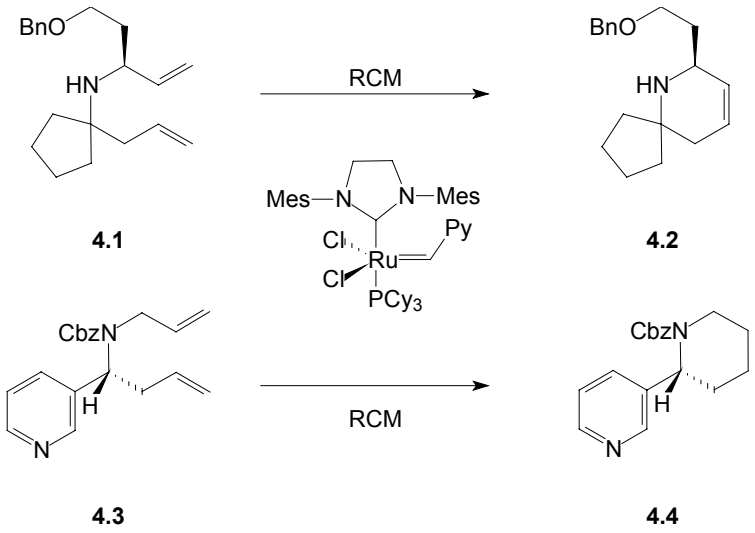


Figure 4.1 *Conversion of protected homoallylamines into topically interesting compounds.*

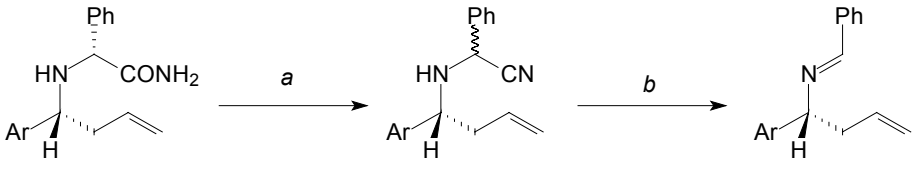
Recently, homoallylamines proved to be key building blocks for the preparation of pyrrolidines and piperidines via a ring closing metathesis (RCM) approach (Scheme 4.1).[3,4]



Scheme 4.1. *Synthesis of **4.2**[3] and **4.4**[4] via a ring closing metathesis.*

4.2 Non-reductive Removal of the Chiral Auxiliary

Because the reductive removal of the chiral auxiliary as described in Chapter 3 failed for some of the adducts, we sought alternative routes for the conversion of the phenylacetamide protected homoallylamines into the desired "free" (*R*)-1-aryl-1-butylamines. In a general procedure, the (*R*)-PGA homoallylamines **3.42–3.59** are converted into *N*-benzylidene protected homoallylamines **4.23–4.40** by "retro-Strecker" methodology as shown schematically in Scheme 4.2.



Scheme 4.2 *Retro-Strecker synthesis of N-benzylidene protected homoallylamines (R)-**4.23–4.40**. Reagents and conditions: (a) Vilsmeier reagent ($[ClCH=N(CH_3)_2^+Cl^-]$, 1.5 equiv.), CH_2Cl_2, NEt_3 (1 equiv.), 0 °C to rt; (b) K_2CO_3 (2 equiv.), EtOH, reflux, 2h.*

Halo-, phenyl-, nitro-, hydroxy- and naphthyl-substituted PGA allylamines have been subjected to this non-reductive deprotection procedure as reported recently.[5c]

The conversion of the PGA protected allylamines (*R,R*)-**3.42**–**3.59** into nitriles **4.5**–**4.22** is based on dehydration of the amide moiety with preformed Vilsmeier reagent [ClCH=N$(CH_3)_2^+Cl^-$] [6] in combination with one equivalent of triethylamine. In a general procedure, the Vilsmeier reagent is formed *in situ* by reaction of DMF with oxalyl chloride in CH_2Cl_2 at 0 °C. A solution of the amide in CH_2Cl_2 is then added to the Vilsmeier reagent. The addition of 1 equivalent of an organic base such as triethylamine drives the formation of the nitrile to completion. Table 4.1 summarizes the results of the formation of the corresponding nitriles.

Although the stereocenter of the chiral auxiliary partially epimerizes under these conditions, the deprotection proceeds with full retention of configuration at the homoallylic stereocenter as revealed by the fact that enantiomerically pure amines are obtained after complete deprotection (Table 4.2, entries 2–7). Although under these conditions the stereocenters of the chiral auxiliary moiety are partially epimerized in nitriles **4.5**–**4.14**, **4.21** and **4.22**, the deprotection proceeds with full retention of configuration at the homoallylic stereocenter as revealed by the fact that enantiomerically pure amines are obtained after complete deprotection (Table 4.2, entries 2–7).

The non-reductive removal failed for nitro-substituted substrates **3.52**–**3.54**, probably because of the sensitive nature of the NO_2-group (Table 4.1, entries 11–13). A complex mixture of products, including starting material, was observed by NMR spectroscopy.

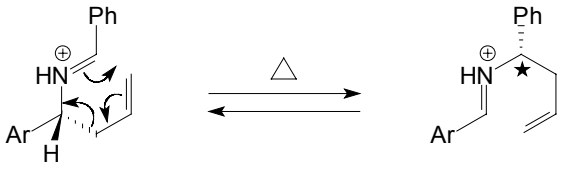
Treatment of hydroxy-substituted PGA homoallylamines **3.55**–**3.57** (entries 14–16) with 1.5 equivalents of Vilsmeier reagent also failed to produce the corresponding nitriles **4.18**–**4.20**. The failure of this reaction is probably due to the relatively acidic phenolic hydroxyl group. Addition of more than one equivalent of triethylamine failed to lead to formation of the desired nitriles. In all cases complex mixtures of products were obtained.

The conversion of nitriles **4.5**–**4.22** into the *N*-benzylidene protected allylamines (*R*)-**4.23**–**4.40** involves the elimination of HCN. Treatment of the crude nitrile with two equivalents of K_2CO_3 for two hours in refluxing ethanol results in full elimination of HCN, providing the benzylidenes in high yields (Scheme 4.2 and Table 4.1). Acidic hydrolysis is usually the method of choice for the deprotection of benzylidene protected amines.[7] To our surprise, these benzylidenes are rather stable in aqueous HCl at ambient temperatures. At elevated temperatures, the benzylidenes are hydrolyzed although aza-Cope rearrangement is a competing reaction (Scheme 4.3).[5a]

Table 4.1 *Formation of nitriles **4.5**–**4.22** by dehydration of the (R)-PGA-moiety and formation of (R)-N-benzylidenes **4.23**–**4.40** by elimination of HCN.*

Entry	Allylamine	Ar	Nitrile	Yield (%)[a]	Benzylidene	Yield (%)[a]
1	**3.42**	C_6H_5	**4.5**	95	**4.23**	86
2	**3.43**	*o*-Cl C_6H_4	**4.6**	87	**4.24**	78
3	**3.44**	*m*-Cl C_6H_4	**4.7**	87	**4.25**	85
4	**3.45**	*p*-Cl C_6H_4	**4.8**	99	**4.26**	86
5	**3.46**	*o*-Br C_6H_4	**4.9**	81	**4.27**	75
6	**3.47**	*m*-Br C_6H_4	**4.10**	92	**4.28**	>99
7	**3.48**	*p*-Br C_6H_4	**4.11**	83	**4.29**	>99
8	**3.49**	*o*-Ph C_6H_4	**4.12**	89	**4.30**	70
9	**3.50**	*m*-Ph C_6H_4	**4.13**	78	**4.31**	69
10	**3.51**	*p*-Ph C_6H_4	**4.14**	80	**4.32**	79
11	**3.52**	*o*-NO_2 C_6H_4	**4.15**	_ [b]	**4.33**	–
12	**3.53**	*m*- NO_2 C_6H_4	**4.16**	_ [b]	**4.34**	–
13	**3.54**	*p*- NO_2 C_6H_4	**4.17**	_ [b]	**4.35**	–
14	**3.55**	*o*-OH C_6H_4	**4.18**	_ [c]	**4.36**	–
15	**3.56**	*m*-OH C_6H_4	**4.19**	_ [c]	**4.37**	–
16	**3.57**	*p*-OH C_6H_4	**4.20**	_ [c]	**4.38**	–
17	**3.58**	1-Naphthyl	**4.21**	80	**4.39**	95
18	**3.59**	2-Naphthyl	**4.22**	80	**4.40**	94

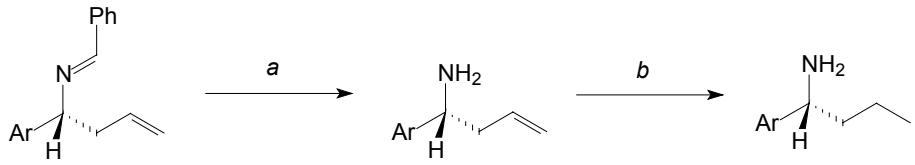
[a] Isolated yield. [b] Mixture of compounds, including starting material. [c] Complex mixture of compounds was obtained.



Scheme 4.3 *Competing aza-Cope rearrangement at elevated temperatures.*[8]

Hydroxylamine hydrochloride in aqueous THF [9] proved to be the reagent of choice for the room temperature hydrolysis of the *N*-benzylidene protected arylbutenylamines (*R*)-**4.23**–**4.40** (Scheme 4.4), which provided the 1-aryl-3-butenylamines (*R*)-**4.41**–**4.52** in yields up to 80 % (Table 4.2).

Scheme 4.4 and Table 4.2 *Synthesis of **4.53**–**4.62** by hydrolysis followed by reduction of **4.23**–**4.40**. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, THF/H_2O, rt; (b) H_2, Pt–C (5 %), EtOAc, 1h.*



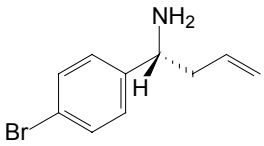
(*R*)-**4.23**-**4.40** (*R*)-**4.41**-**4.52** (*R*)-**4.53**-**4.62**

Entry	Benzyl Idene	Ar	Butenyl amine	Yield (%)[a]	Butyl amine	Yield (%)[a]	*er* (*R*):(*S*)[b]
1	**4.23**	C_6H_5	**4.41**	80	**3.64**	*nd*	*nd*
2	**4.24**	*o*-Cl C_6H_4	**4.42**	75	**4.53**	91	>99:1
3	**4.25**	*m*-Cl C_6H_4	**4.43**	58	**4.54**	>99	>99:1
4	**4.26**	*p*-Cl C_6H_4	**4.44**	70	**4.55**	>99	>99:1

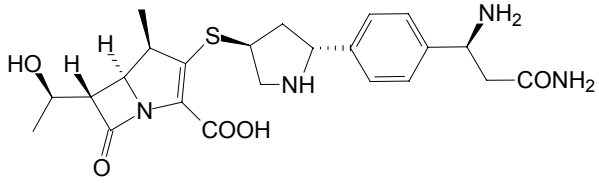
Entry	Benzyl Idene	Ar	Butenyl amine	Yield (%)[a]	Butyl amine	Yield (%)[a]	*er* (*R*):(*S*)[b]
5	**4.27**	*o*-Br C_6H_4	**4.45**	65	**4.56**	99	>99:1
6	**4.28**	*m*-Br C_6H_4	**4.46**	51	**4.57**	>99	>99:1
7	**4.29**	*p*-Br C_6H_4	**4.47**	48	**4.58**	85	>99:1
8	**4.30**	*o*-Ph C_6H_4	**4.48**	57	**3.74**	*nd*	*nd*
9	**4.31**	*m*-Ph C_6H_4	**4.49**	45	**4.59**	93	*nd*
10	**4.32**	*p*-Ph C_6H_4	**4.50**	49	**4.60**	95	*nd*
11	**4.39**	1-naphthyl	**4.51**	60	**4.61**	>99	*nd*
12	**4.40**	2-naphthyl	**4.52**	47	**4.62**	>99	*nd*

[a] Isolated yield. [b] Analysis by HPLC.[10] *nd*: Not determined.

As the allylic moiety is preserved in this non-reductive procedure, valuable homoallylamines like **4.41**–**4.52** could be obtained in overall yields up to 65 % (3 steps). An example of the synthetic value of this methodology is the synthesis of (*R*)-1-*para*-bromophenyl-3-butylenamine **4.47**. This chiral homoallylamine is a useful building block in the total synthesis of a novel antimicrobial 1β-methyl carbapenem **4.63**.[11]



(*R*)-**4.47**

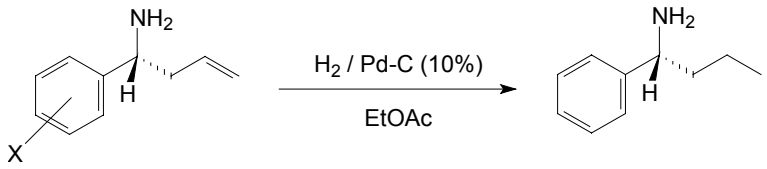


4.63

With satisfactory results for the synthesis of the arylbutenylamines (*R*)-**4.41**–**4.52** in hand, we undertook further reduction of the double bond by catalytic hydrogenation with H_2 in the presence of 5 % platinum on carbon,[12] which gave the corresponding saturated substituted 1-arylbutylamines (*R*)-**4.53**–**4.62** in almost quantitative yields (Scheme 4.2, Table 4.2). Samples were taken during the reaction and analyzed by ^{1}H- and ^{13}C-NMR to follow the reaction; after one hour the uptake of 1 mole equivalent of H_2 was complete. In

case of reduction of the bromo-substituted phenylbutenylamines (*R*)-**4.45**–**4.47** (entries 5–7) high yields of the saturated butylamines **4.56**–**4.58** were obtained. The loss of the bromo-substituents has not been observed if the hydrogenation time was limited to one hour at ambient temperature. However, longer reaction times also resulted in a considerable amount of the dehalogenated products.

The undesired dehalogenation in the reductive removal of the chiral auxiliary, as described in Chapter 3 (section 3.2.2), can be used to our advantage. For *ee*-determination by HPLC analysis, the chloro- and bromo-substituted 1-aryl-3-butylamines **4.53**–**4.58** were all dehalogenated into 1-phenyl-1-butylamine **3.64** with H_2 and 10 % palladium on carbon in EtOAc (Scheme 4.5). The high enantiomeric ratios (*er*) of these chiral amines (Table 4.2, entries 2–7) determined by this general HPLC method again confirmed the diastereoselectivity of the allylation reaction and lack of racemization of the phenylglycine amide moiety.



X = Br, Cl

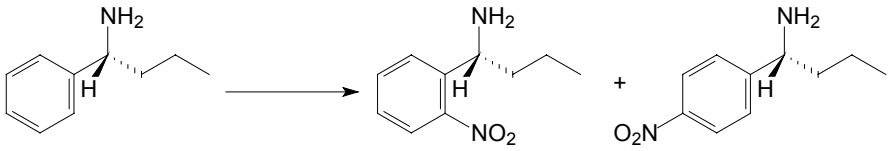
(*R*)-**4.53**-**4.58** (*R*)-**3.64**

Scheme 4.5 *Dehalogenation and reduction of **4.53**–**4.58** into **3.64** for ee-determination by HPLC analysis.*

4.3 Synthesis of Nitro-substituted Phenylbutylamines

Owing to the failure of both reductive as non-reductive removal towards the nitro-substituted phenylbutylamines an alternative method was examined. Nitration of enantiomerically pure 1-phenyl-1-butylamine (*R*)-**3.64** with nitric acid[13] provided a mixture containing (*R*)-1-*ortho*-nitrophenyl-1-butylamine [(*R*)-**4.64**] and (*R*)-1-*para*-nitrophenyl-1-butylamine [(*R*)-**4.65**] in a ratio of 22:78 (Scheme 4.6). This mixture of regio-isomers was used without further separation.

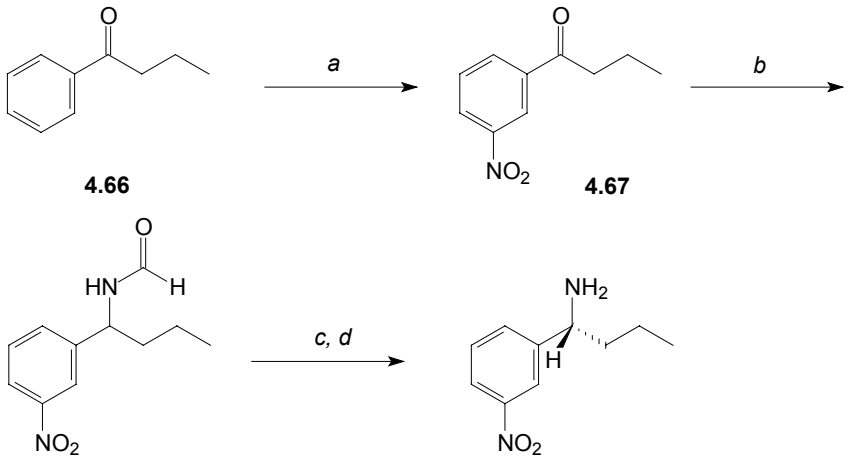
The *meta*-nitro-substituted 1-phenyl-1-butylamine (*R*)-**4.69** was prepared starting from commercially available butyrophenone **4.66** (Scheme 4.7). The *m*-nitrobutyrophenone **4.67** was obtained by nitration of butyrophenone **4.66** with HNO_3 (85 %).[14] The best yield of **4.67** was obtained by nitration at –5 °C.



(*R*)-**3.64** (*R*)-**4.64** 22% (*R*)-**4.65** 78%

Scheme 4.6 *Nitration of enantiopure (R)-1-phenyl-1-butylamine **3.64**. Reagents and conditions: HNO_3 (85 %), –5 °C, 4h.*

The main product was the *meta*-nitro-compound, which is generally accompanied by a small and variable amount of the *ortho*-isomer. The *meta*-nitro compound is easily separated from this mixture by crystallization and obtained pure in 55 % isolated yield. Subsequently, primary amine **4.69** was synthesized by a Leuckart reductive amination of **4.67**, followed by resolution of racemic **4.69** (section 4.4 of this chapter). In the first step of the Leuckart reaction, the imine is formed *in situ* with formamide ($HCONH_2$) followed by a reduction with formic acid. The obtained formamide **4.68** is subsequently hydrolyzed with 10 % HCl and affords the racemic free amine **4.69** in a quantitative yield.



4.66 **4.67** (±)-**4.68** (*R*)-**4.69**

Scheme 4.7 *Reagents and conditions: (a) HNO_3 (85 %), –5 °C, 4h ; (b) $HCONH_2/HCO_2H$, Δ; (c) HCl, Δ; (d) (+)-Phencyphos **4.70**/(+)-Nitrocyphos **4.73** (90:10), 2-butanone/H_2O, Δ, Analysis by HPLC.*[10]

4.4 Dutch Resolution of *Meta*-nitro-phenylbutylamine

Subsequently, the racemic *meta*-nitro-phenylbutylamine needed to be resolved. Several test experiments (1 mmol) were performed,[15] establishing that *meta*-nitro-phenylbutylamine **4.69** could successfully be resolved with the cyclic phosphoric acid (*S*)-(+)-**4.70**, known by the trivial name of Phencyphos. The structures of Phencyphos and some of its family members are given in Figure 4.2.[16,17] Note that all (+)-enantiomers are homochiral; because of Cahn-Ingold-Prelog priority rules (CIP-rules) for the various aromatic substituents, the priority may change from (*S*) to (*R*).

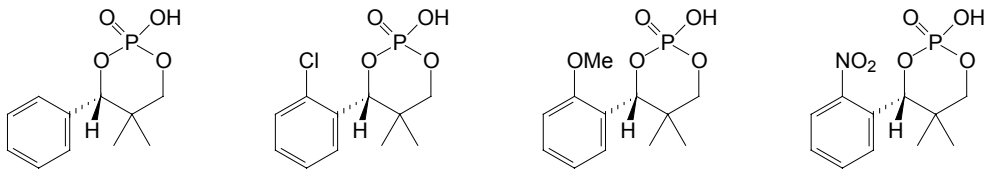


Figure 4.2 *Family of structurally related cyclic phosphoric acids and their trivial names.*[16]

As the absolute configuration of the Phencyphos moiety was known, X-ray crystallographic analysis unambiguously showed that after resolution with (*S*)-(+)-**4.70**, the chiral center C21 of **4.69** had the (*R*)-configuration (Figure 4.3).[18]

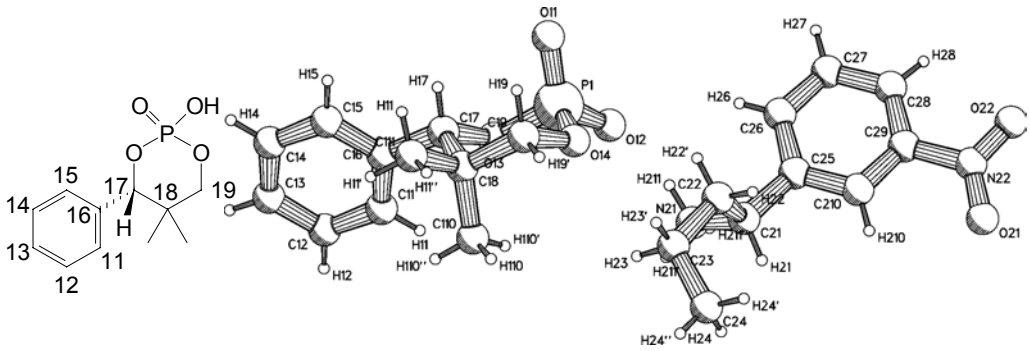
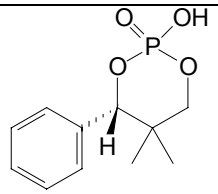
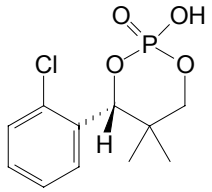
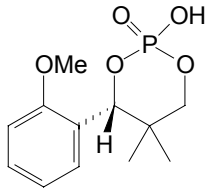
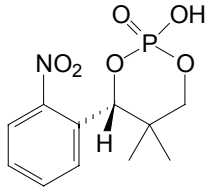


Figure 4.3 *Structure of (S)-(+)-Phencyphos **4.70** and crystal structure of (S)-**4.70**/(R)-**4.69**.*

The resolution of racemic *meta*-nitro-phenylbutylamine **4.69** with (*S*)-(+)-Phencyphos in the absence of an additive delivered a first salt with a *de* value of 34 % and an S-factor[19] of 0.30 (Table 4.3, entry 1). Under the same conditions, resolution with (+)-Chlocyphos as the parent resolving agent resulted in the precipitation of a salt with no diastereoselectivity (entry 2). In both cases, resolution experiments with either Anicyphos or Nitrocyphos failed to produce precipitated salts (entries 3 and 4).

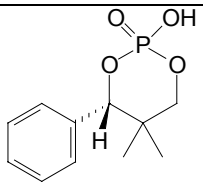
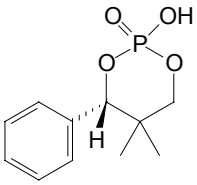
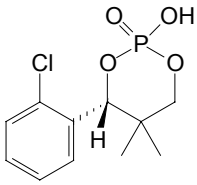
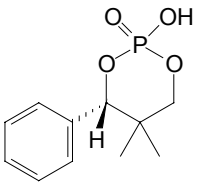
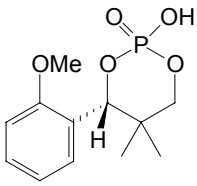
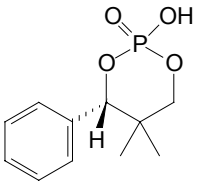
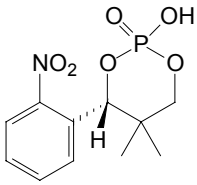
Table 4.3 *Resolution of meta-nitro-phenylbutylamine **4.69** with one member of the cyclic phosphoric acid family **4.70**–**4.73** as the resolving agent.*

Entry	Resolving Agent	Solvent[a]	Yield (%)[b]	*de* (%)[c]	*S* Factor[d]
1		2-butanone/H_2O (2:1)	44	34	0.30
2		2-butanone/H_2O (2:1)	26	1	0
3		2-butanone/H_2O (2:1)	*no salts precipitates*		
4		2-butanone/H_2O (2:1)	*no salts precipitates*		

[a] 033 mmol·mL^{-1} in 2-butanone:H_2O (2:1). [b] Isolated yield of the first salt. [c] *de* of the first isolated salt.[12] [d] S = 2 × yield × *de*.[19]

Several experiments were performed, analogous to the second generation Dutch Resolution experiments described by Nieuwenhuijzen *et al.*[20] The resolution process could be considerably improved on replacement of 10 mol % of (+)-Phencyphos by one of the structurally closely related family members depicted in Figure 4.2. On substitution by 10 mol % of (+)-Chlocyphos **4.71**, the *de* value increases from 34 % to 67 % (Table 4.4, entry 2). (+)-Chlocyphos **4.71** itself gave first salts with lower *de*'s. In the presence of 10 mol % of (+)-Anicyphos **4.72** or (+)-Nitrocyphos **4.73**, the de value of the first isolated salt increases to 78 % and 77 % respectively, and the S-factor increases to respectively 0.58 and 0.59 (entries 3 and 4).

Table 4.4 *Resolution of meta-nitro-phenylbutylamine* ***4.69*** *in the presence of a family member of the resolving agent.*

Entry	Resolving Agent	Additive	Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[c]
1		–		44	34	0.30
2			10	39	67	0.52
3			10	37	78	0.58
4			10	38	77	0.59

[a] Isolated yield of the first salt. [b] *de* of the first isolated salt.[12] [c] S = 2 × yield × *de*.[19]

The amount of the additives **4.71**-**4.73** present in the salt could be readily determined by ^{1}H-NMR spectroscopy. Analysis of the ^{1}H-NMR spectra in the region of 5.0–5.6 ppm revealed that the benzylic proton (indicated as *a* in Figure 4.5) of the Phencyphos part of the salt gives rise to a doublet at δ = 5.00 ppm, while the benzylic protons of the substituted cyclic phosphoric acids (indicated as *a'*) resonate typically at lower field (5.45–5.60 ppm). By comparing the integrals of both signals, the ratio could be determined. A practical example of this determination by ^{1}H-NMR is given in Figure 4.4.

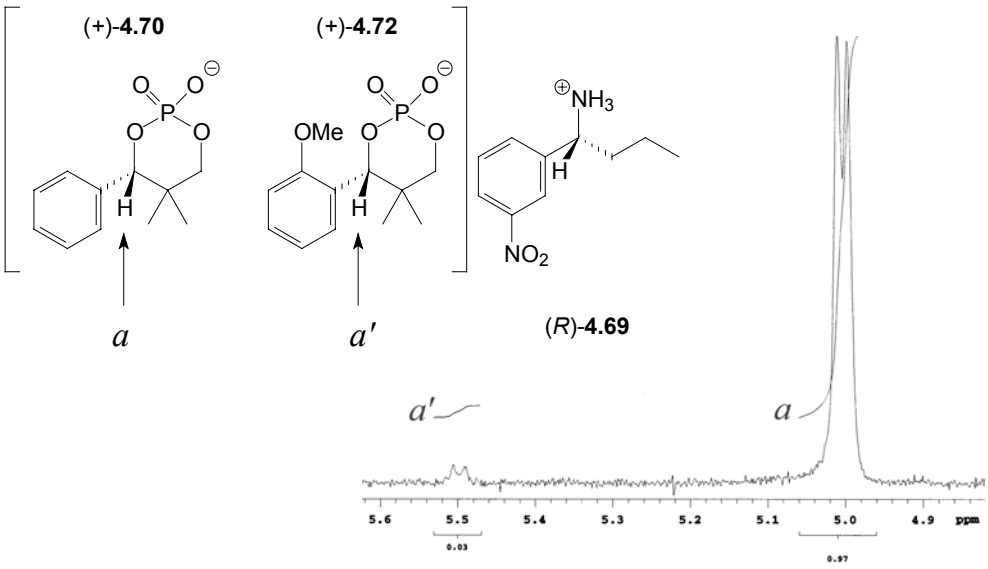
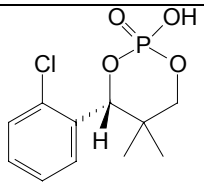
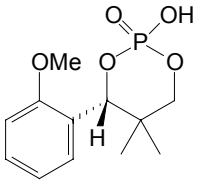
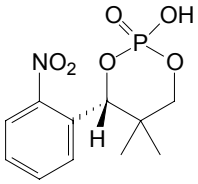


Figure 4.4 *Example of determination of the amount of additive in the salt by ^{1}H-NMR spectroscopy in the case of Anicyphos **4.72** as an additive.*

It was found that in the precipitation of the first salts, in the cases of Chlocyphos and Anicyphos, the additives were present in a smaller amount than the initial amounts started with (Table 4.5, entries 1 and 2). In the case of Nitrocyphos as a family member, no detectable amount of the additive was incorporated in the salt (entry 3).[21]

Recrystallization of the mixed salts resulted in a shift in composition; after one recrystallization from *i*-propanol/H_2O (2:1) (entries 1 and 2) a salt was obtained which only contained Phencyphos as the anionic counter-ion. No detectable amounts of the additives were found in the salt.[21]

Table 4.5 *Amount of additive present in the salts in the resolution of* ***4.69****.*

Entry	Ar	Amount in first isolated salt [a]	Amount after 1 recrystallization [a]
1		7 %	0 %
2		3 %	0 %
3		0 %	–

[a] Determined by ^{1}H-NMR.

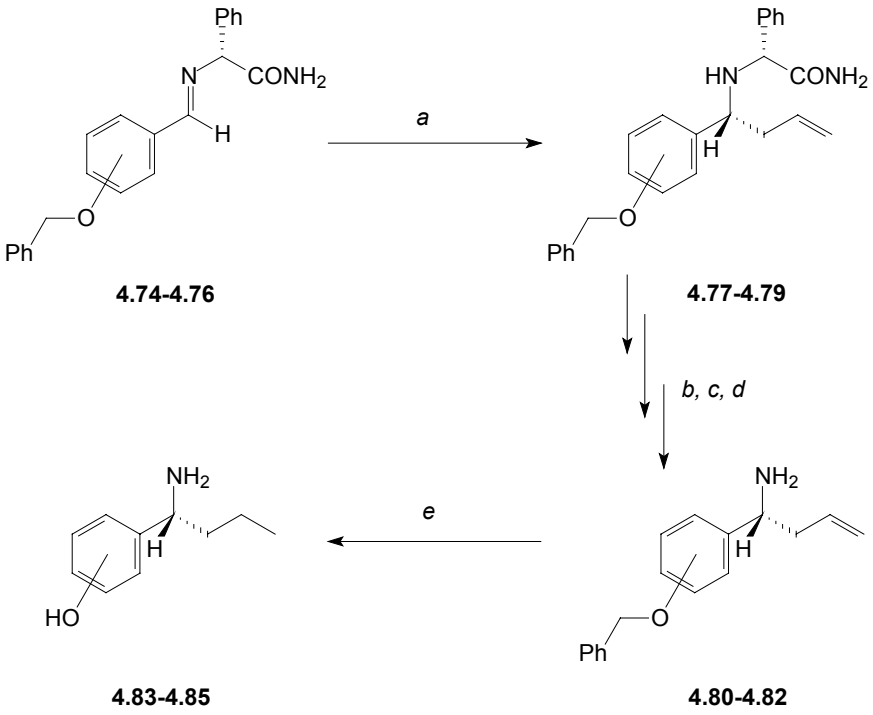
In large scale experiments (80 mmol), the resolution was performed in the presence of the non-incorporated Nitrocyphos. Since Nitrocyphos was not found in the first isolated salt, the parent resolving agent could be easily recycled. After one recrystallization of the first obtained salt from *i*-propanol/H_2O (2:1) and liberation, the free amine (*R*)-**4.69** was obtained in 24 % yield and > 99 % *ee* (limit of detection).

4.5 Proposed Synthesis of Hydroxy-substituted Phenylbutylamines

As mentioned earlier in this chapter, the conversion of the hydroxy substituted PGA allylamines **3.55**–**3.57** into nitriles **4.18**–**4.20** failed, probably due to the presence of the relatively acidic phenolic hydroxyl group.

A plausible route to the desired hydroxy substituted phenylbutylamines is proposed in Scheme 4.8. In this strategy, *O*-benzyl protected imines **4.74**–**4.76** can be synthesized from the corresponding commercially available *O*-benzyl benzaldehydes. After diastereoselective allylation (step *a*), *O*-benzyl protected PGA allylamines **4.77**–**4.79** can be subjected to the non-reductive removal of the chiral auxiliary as described in this chapter

(steps *b–d*), providing homoallylamines **4.80**–**4.82**. Because in **4.78**–**4.79** the acidic phenolic hydroxyl group is protected, the non-reductive removal might be successful.



Scheme 4.8 *Proposed synthetic route to the hydroxy-substituted 1-phenyl-1-butylamines **4.83–4.85**. (a) Diastereoselective allylation; (b–d) non-reductive removal of the PGA auxiliary; (e) O-debenzylation and reduction of the allylic moiety.*

It is well known in the literature that *O*-benzyl ether protecting groups are easily removed under hydrogenolysis conditions (H_2/Pd-C); compounds **4.80**–**4.82** most probably will be no exception (step *e*).[7,22] Catalytic hydrogenolysis of *O*-benzyl protected homoallylamines **4.80**–**4.82** would lead to catalytic debenzylation as well as the hydrogenation of the allylic moiety, providing the desired hydroxy-substituted 1-phenyl-1-butylamines **4.83**–**4.85**. Removal of the benzyl ethers with sodium/ammonia might leave the double bond intact, yielding the unsaturated hydroxy substituted 1-phenyl-3-butenylamines.[23] We have not had the opportunity to try this route in the laboratory.

4.6 Conclusions

This chapter further illustrates the versatility of (*R*)-PGA allyl amines in the synthesis of topically interesting amines bearing a stereogenic center at the α–position. The chiral auxiliary is conveniently removed under either reductive- or non-reductive conditions.

The problems we encountered with the reductive removal of the chiral auxiliary in the synthesis of the bromo-, chloro-substituted and naphthyl amines could be overcome. In the mild reduction of the 1-naphthyl-3-butenylamines with H_2/Pt-C, no ring hydrogenation was observed.

The high enantiomeric ratios (*er*) of **4.53**–**4.57** again confirm the high diastereoselectivities of the allylation reaction and lack of racemization of the phenylglycine amide moiety.

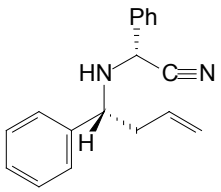
The sensitivity of the hydroxy- and the nitro-group prevented the synthesis of the desired substituted phenylbutylamines using the reductive- or non-reductive removal of the chiral auxiliary. Alternative routes were used to synthesize the nitro-substituted 1-aryl-1-butylamines. An alternative route has been proposed to synthesize the hydroxy substituted analogues.

4.7 Experimental Section

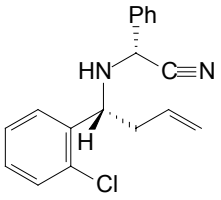
General information: For general remarks concerning all experimental details see experimental section in Chapter 3.

Typical procedure for the formation of nitriles 4.23–4.40.[5c] To dichloromethane (450 mL), cooled in an ice bath, was added dimethylformamide (48.8, mmol, 3.79 mL). Oxalyl chloride (48.8 mmol, 4.60 mL) was added dropwise. After the formation of gas (CO and CO_2) had ceased, the (*R*,*R*)-PGA allylamine (32.5 mmol) dissolved in dichloromethane (100 mL) was added all at once. Triethylamine (32.5 mmol, 4.60 mL) was added dropwise over 30 minutes and the reaction was stirred at room temperature for 30 minutes. Water (450 mL) was added and the organic phase was separated. The organic layer was dried over Na_2SO_4 and filtered. Evaporation of the solvent yielded the crude product, which was used without further purification.

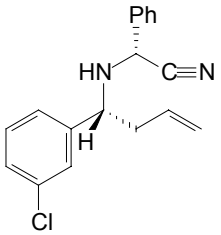
From the mixture of diastereomers, only the most abundant is described.



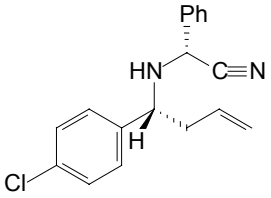
(2*R*)-2-{[(1*R*)-1-phenyl-3-butenyl]amino}-2-phenyl ethane nitrile (4.5): (orange oil, 95 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.27–2.51 (m, 2H), 2.92 (brs, 1H), 4.06 (dd, J = 8.42, J = 4.76 Hz, 1H), 4.35 (s, 1H), 4.98–5.10 (m, 2H), 5.66–5.78 (m, 1H), 6.95–7.43 (m, 10H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.84 (t), 51.93 (d), 60.41 (d), 118.56 (t), 118.64 (s), 126.96 (d), 127.24 (d), 127.82 (d), 128.48 (d), 128.74 (d), 130.24 (d), 134.24 (d), 134.89 (s), 141.36 (s) ppm. MS (CI): m/z = 263 [M + H$^+$].



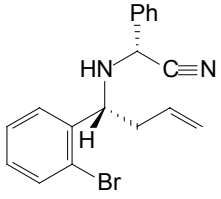
(2*R*)-2-{[(1*R*)-1-(2-chlorophenyl)-3-butenyl]amino}-2-phenyl ethanenitrile (4.6): (orange oil, 87 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.16–2.60 (m, 2H), 2.82 (brs, 1H), 4.26 (t, J = 7.69 Hz, 1H), 4.66 (s, 1H), 4.95–5.12 (m, 2H), 5.70–5.83 (m, 1H), 7.11–7.73 (m, 9H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 41.16 (t), 52.10 (d), 56.08 (d), 117.48 (s), 118.87 (s), 119.03 (t), 127.04 (d), 127.28 (d), 127.62 (d), 128.29 (d), 128.66 (d), 128.92 (d), 129.99 (d), 134.13 (d), 138.74 (s), 150.95 (s) ppm. MS (CI): *m/z* = 297 (58.4) [M + H$^+$], 299 (20.9) [M + H$^+$].



(2*R*)-2-{[(1*R*)-1-(3-chlorophenyl)-3-butenyl]amino}-2-phenyl ethanenitrile (4.7): (orange oil, 87 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.01 (brs, 1H), 2.29–2.51 (m, 2H), 4.06 (dd, J = 8.61, J = 4.94 Hz, 1H), 4.37 (s, 1H), 5.04–5.12 (m, 2H), 5.65–5.79 (m, 1H), 7.18–7.44 (m, 9H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.79 (t), 52.08 (d), 60.09 (d), 118.50 (s), 119.08 (t), 125.62 (d), 127.03 (d), 127.40 (d), 128.11 (d), 128.90 (d), 128.95 (d), 130.08 (d), 133.89 (d), 134.65 (s), 134.71 (s), 143.76 (s) ppm. MS (CI): *m/z* = 297 (100.0) [M + H$^+$], 299 (35.2) [M + H$^+$].

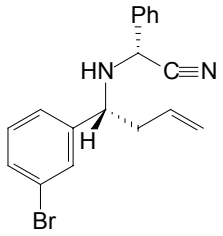


(2*R*)-2-{[(1*R*)-1-(4-chlorophenyl)-3-butenyl]amino}-2-phenyl ethanenitrile (4.8): (orange oil, 99 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.34–2.46 (m, 2H), 2.90 (brs, 1H), 4.04 (dd, J = 8.24, J = 5.31 Hz, 1H), 4.31 (s, 1H), 4.96–5.01 (m, 2H), 5.61–5.75 (m, 1H), 6.93–7.10 (m, 1H), 7.19–7.38 (m, 8H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.75 (t), 51.94 (d), 59.84 (d), 118.47 (s), 118.94 (t), 126.96 (d), 128.65 (d), 128.83 (d), 128.92 (d), 133.43 (s), 133.92 (d), 134.62 (s), 139.94 (s) ppm. MS (CI): *m/z* = 297 (56.9) [M + H$^+$], 299 (24.1) [M + H$^+$].

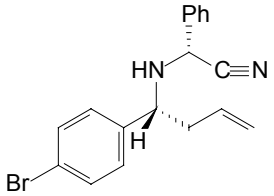


(2*R*)-2-{[(1*R*)-1-(2-bromophenyl)-3-butenyl]amino}-2-phenyl ethanenitrile (4.9): (orange oil, 81 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.10–2.65 (m, 2H), 4.36 (s, 1H), 4.61 (dd, J = 9.15, J = 4.02 Hz, 1H), 4.99–5.21 (m, 1H), 5.52–5.63 (m, 2H), 6.68 (d, J = 8.06 Hz, 2H), 6.88 (d, J = 8.42 Hz, 2H), 7.00–7.60 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 41.18 (t), 51.96 (d), 59.64 (d), 119.00 (t), 119.16 (s), 124.62 (s), 126.96 (d), 127.86 (d), 128.37 (d), 128.84 (d), 129.88 (d), 130.11 (s), 131.89 (d), 133.62 (d), 140.17 (s) ppm. MS (CI): *m/z* = 341 (64,2) [M + H$^+$], 343 (63.8) [M + H$^+$].

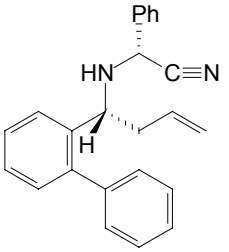
(2*R*)-2-{[(1*R*)-1-(3-bromophenyl)-3-butenyl]amino}-2-phenyl ethanenitrile (4.10): (orange oil, 92 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.97 (brs, 1H), 2.23–2.49 (m, 2H), 4.03 (dd, J = 8.79, J = 4.76 Hz, 1H), 4.35 (s, 1H), 4.98–5.13 (m, 2H), 5.62–5.76 (m, 1H), 6.93–7.43 (m, 8H), 7.58 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 35.76 (t), 42.84 (t), 52.11 (d), 60.06 (d), 119.15 (s), 122.97 (s), 126.09 (d), 127.05 (d), 128.42 (d), 128.97 (d), 130.14 (d), 130.41 (d), 131.16 (d), 133.91 (d), 134.57 (s), 144.07 (s) ppm. MS (CI): *m/z* = 341 (64.2) [M + H$^+$], 343 (65.3) [M + H$^+$].



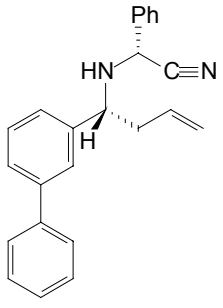
(2*R*)-2-{[(1*R*)-1-(4-bromophenyl)-3-butenyl]amino}-2-phenyl ethanenitrile (4.11): (yellow oil, 83 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.97 (brs, 1H), 2.32–2.40 (m, 2H), 2.42–2.50 (m, 2H), 4.04 (dd, J = 8.79, J = 5.13 Hz, 1H), 4.33 (s, 1H), 4.98–5.10 (m, 2H), 5.63–5.77 (m, 1H), 7.21–7.42 (m, 7H), 7.47 (d, J = 8.42 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.84 (t), 52.10 (d), 57.34 (d), 97.96 (t), 119.08 (s), 127.07 (d), 128.95 (d), 129.00 (d), 129.11 (d), 132.01 (d), 133.98 (d), 137.86 (s), 137.97 (s), 150.99 (d), 160.82 (s) ppm. MS (CI): *m/z* = 341 (100.0) [M + H$^+$], 343 (97.4) [M + H$^+$].



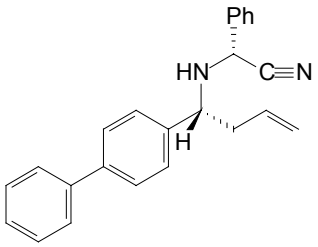
(2*R*)-2-{[(1*R*)-1-[1,1'-biphenyl]-2-yl-3-butenyl]amino}-2-phenyl ethanenitrile (4.12): (red oil, 78 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.12–2.42 (m, 2H), 4.26 (dd, J = 6.95, J = 4.03 Hz, 1H), 4.43 (s, 1H), 4.89–5.00 (m, 2H), 5.47–5.61 (m, 1H), 7.16–7.43 (m, 14H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 42.55 (q), 51.62 (d), 55.39 (d), 118.54 (s), 118.89 (s), 125.93 (d), 127.02 (d), 127.24 (d), 127.99 (d), 128.15 (d), 128.77 (d), 129.31 (d), 129.85 (d), 130.04 (d), 130.24 (d), 135.16 (s), 139.04 (s), 140.38 (s), 142.78 (s) ppm. MS (CI): *m/z* = 339 (M + H$^+$).



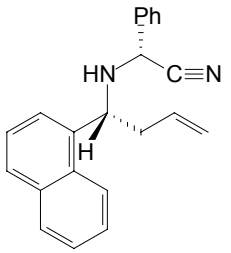
(2*R*)-2-{[(1*R*)-1-[1,1'-biphenyl]-3-yl-3-butenyl]amino}-2-phenyl ethanenitrile (4.13): (orange oil, 78 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.32–2.54 (m, 2H), 4.14 (dd, J = 8.43, J = 5.12 Hz, 1H), 4.42 (s, 1H), 5.00–5.18 (m, 2H), 5.68–5.81 (m, 1H), 7.29–7.49 (m, 11H), 7.56 (d, J = 8.06 Hz, 2H), 7.65 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.71 (t), 51.89 (d), 60.43 (d), 118.51 (t), 125.85 (d), 125.98 (d), 126.47 (d), 126.85 (d), 127.19 (d), 128.56 (d), 128.63 (d), 129.08 (d), 134.20 (d), 134.76 (s), 140.52 (s), 141.44 (s), 141.89 (s) ppm. MS (CI): *m/z* = 339 [M + H$^+$].



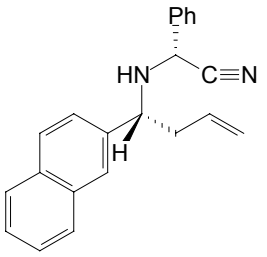
(2*R*)-2-{[(1*R*)-1-[1,1'-biphenyl]-4-yl-3-butenyl] amino}-2-phenyl ethanenitrile (4.18): (orange oil, 80 % yield). ^{1}H-NMR (300MHz, [D_6]DMSO): δ = 2.83–3.16 (m, 2H), 3.41 (brs, 1H), 4.00 (t, J = 6.60 Hz, 1H), 4.49 (s, 1H), 4.97–5.08 (m, 2H), 5.58–5.79 (m, 1H), 7.12–7.49 (m, 10H), 7.60–7.70 (m, 4H) ppm. ^{13}C-NMR (50MHz, [D_6]DMSO): δ = 34.30 (t), 50.04 (d), 59.61 (d), 117.38 (s), 119.35 (s), 126.59 (d), 126.82 (d), 127.28 (d), 128.51 (d), 128.66 (d), 128.91 (d), 128.97 (d), 129.76 (d), 131.08 (s), 134.90 (d), 135.70 (s), 139.29 (t), 140.89 (s) ppm. MS (CI): m/z = 339 ($M + H^+$).



(2*R*)-2-{[(1*R*)-1-(1-naphthyl)-3-butenyl]amino}-2-phenyl ethanenitrile (4.21): (orange oil, 80 % yield). ^{1}H-NMR (300MHz, [D_6]DMSO) δ = 2.71–3.02 (m + brs, 3H) 4.67 (s, 1H), 4.98–5.20 (m + t, 3H), 5.80–5.94 (m, 1H), 7.34–7.56 (m, 8H), 7.78–7.89 (m, 4H) ppm. ^{13}C-NMR (50MHz, [D_6]DMSO) δ = 52.18 (d), 77.42 (t), 125.54 (d), 125.65 (d), 126.12 (d), 127.04 (d), 128.26 (d), 128.42 (d), 128.82 (d), 128.97 (d), 131.43 (s), 134.11 (s), 134.58 (d), 134.97 (s), 150.86 (d) ppm. MS (CI): m/z = 313 ($M + H^+$).

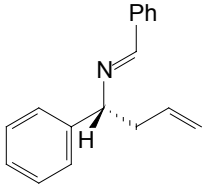


(2*R*)-2-{[(1*R*)-1-(2-naphthyl)-3-butenyl]amino}-2-phenyl ethanenitrile (4.22): (orange oil, 80 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.43–2.64 (m, 2H), 2.87 (brs, 1H), 4.26 (dd, J = 8.09, J = 4.94 Hz, 1H), 4.38 (s, 1H), 5.03–5.15 (m, 2H), 5.70–5.84 (m, 1H), 7.23–7.87 (m, 12H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 42.66 (t), 52.11 (d), 60.74 (d), 118.72 (t), 124.61 (d), 125.97 (d), 126.32 (d), 126.86 (d), 127.06 (d), 127.58 (d), 127.64 (d), 127.80 (d), 128.81 (d), 128.85 (d), 133.24 (s), 133.28 (s), 134.36 (d), 134.97 (s), 138.78 (s) ppm. MS (CI): m/z = 313 ($M + H^+$).

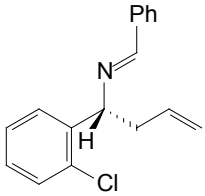


Typical procedure for the retro-Strecker formation of the benzylidene protected amines 4.23–4.34. Nitrile **4.5–4.22** (32.5 mmol) was dissolved in ethanol (150 mL). After the addition of K_2CO_3 (2 equiv.; 64.9 mmol; 8.97 gram), the reaction mixture was refluxed for two hours. After cooling the reaction mixture to room temperature, the solvent was evaporated. The residue was mixed with water (100 mL) and dichloromethane (100 mL). The organic phase was separated, dried over Na_2SO_4 and filtered. Removal of the solvent furnishes the crude *N*-benzylidene derivatives as oily materials, which was used without further purification.

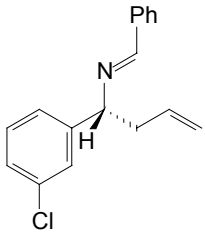
(1*R*)-1-phenyl-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.23): (orange oil, 86 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.67 (t, J = 6.95 Hz, 2H), 4.32 (t, J = 6.95 Hz, 1H), 4.96–5.14 (m, 2H), 5.61–5.77 (m, 1H), 7.21–7.43 (m, 8H), 7.75 (dd, J = 6.59, J = 3.30 Hz, 2H), 8.27 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 43.10 (d), 75.26 (d), 117.12 (t), 126.92 (d), 127.00 (d), 128.33 (d), 128.43 (d), 130.50 (d), 135.38 (d), 136.22 (s), 143.75 (s), 159.95 (d) ppm. MS (CI): *m/z* = 236 [M + H$^+$].



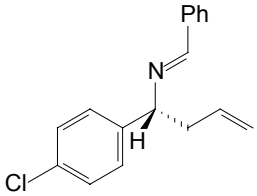
(1*R*)-1-(2-chlorophenyl)-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.24): (orange oil, 78 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.56–2.70 (m, 2H), 4.83 (t, J = 6.96 Hz, 1H), 4.98–5.09 (m, 2H), 5.66–5.80 (m, 1H), 7.13–7.37 (m, 7H), 7.72–7.81 (m, 2H), 8.30 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 41.72 (t), 70.43 (d), 117.48 (t), 126.91 (d), 128.29 (d), 127.80 (d), 128.47 (d), 128.82 (d), 129.31 (d), 130.63 (d), 132.37 (s), 134.96 (d), 136.14 (s), 141.15 (s), 160.88 (d) ppm. MS (CI): *m/z* = 270 (100.0) [M + H$^+$], 272 (33.4) [M + H$^+$].



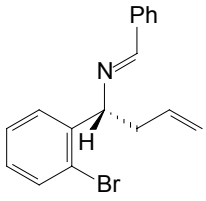
(1*R*)-1-(3-chlorophenyl)-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.25): (orange oil, 85 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.61 (t, J = 6.96 Hz, 2H), 4.26 (t, J = 6.96 Hz, 1H), 4.96–5.02 (m, 2H), 5.58–5.72 (m, 1H), 7.15–7.42 (m, 7H), 7.74 (dd, J = 5.85, J = 2.19 Hz, 2H), 8.24 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 43.15 (t), 74.69 (d), 117.57 (t), 120.12 (s), 125.50 (d), 127.07 (d), 127.20 (d), 128.32 (d), 128.51 (d), 129.58 (d), 130.73 (d), 134.15 (s), 134.84 (d), 145.86 (s), 160.41 (d) ppm. MS (CI): *m/z* = 270 (100.0) [M + H$^+$], 272 (34.3) [M + H$^+$].



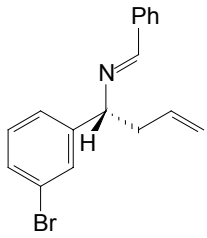
(1*R*)-1-(4-chlorophenyl)-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.26): (orange oil, 86 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.61 (dt, J = 6.96 Hz, 2H), 4.28 (t, J = 6.96 Hz, 1H), 4.96–5.05 (m, 2H), 5.56–5.73 (m, 1H), 7.26 (d, J = 8.42 Hz, 2H), 7.34–7.36 (m, 5H), 7.72–7.75 (m, 2H), 8.25 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 43.13 (t), 74.43 (d), 117.47 (t), 128.13 (d), 128.22 (d), 128.34 (d), 128.40 (d), 128.45 (d), 130.63 (d), 132.48 (s), 134.86 (d), 136.02 (s), 142.24 (s), 160.17 (d) ppm. MS (CI): *m/z* = 270 (100.0) [M + H$^+$], 272 (34.2) [M + H$^+$].



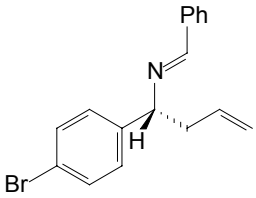
(1*R*)-1-(2-bromophenyl)-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.27): (orange oil, 75 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.47–2.69 (m, 2H), 4.77 (dd, J = 8.2, J = 4.6 Hz, 1H), 4.97–5.10 (m, 2H), 5.62–5.80 (m, 1H), 6.94–7.50 (m, 6H), 7.73–7.76 (m, 2H), 8.29 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 41.67 (t), 72.85 (d), 117.53 (t), 126.39 (d), 127.49 (s), 127.52 (d), 128.05 (d), 128.25 (d), 128.27 (d), 129.75 (d), 130.63 (d), 133.15 (d), 131.71 (d), 142.68 (s), 160.81 (d) ppm. MS (CI): *m/z* = 314 (100.0) [M + H$^+$], 316 (99.1) [M + H$^+$].



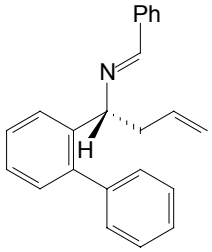
(1*R*)-1-(3-bromophenyl)-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.28): (orange oil, >99 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.94 (t, J = 7.08 Hz, 2H), 4.30 (t, J = 6.83 Hz, 1H), 4.99–5.22 (m, 2H), 5.44–5.84 (m, 1H), 7.00–7.45 (m, 8H), 7.70–7.81 (m, 1H), 8.23 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 36.10 (t), 74.64 (d), 117.60 (d), 118.24 (s), 118.67 (s), 125.65 (d), 128.16 (d), 128.31 (d), 129.99 (d), 130.12 (d), 130.43 (d), 130.72 (d), 134.80 (d), 146.23 (s), 160.41 (d) ppm. MS (CI): *m/z* = 314 (100.0) [M + H$^+$], 316 (94.2) [M + H$^+$].



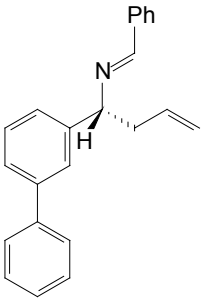
(1*R*)-1-(4-bromophenyl)-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.29) : (red oil, >99 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.64 (t, J = 6.84 Hz, 2H), 4.30 (t, J = 6.96 Hz, 1H), 4.98–5.16 (m, 2H), 5.79–5.44 (m, 1H), 7.45–7.29 (m, 7H), 7.77 (dd, J = 6.11, J = 2.44 Hz, 2H), 8.29 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 43.13 (t), 74.53 (d), 117.51 (t), 124.79 (d), 126.65 (s), 128.16 (d), 128.26 (d), 128.48 (d), 128.66 (d), 128.76 (d), 130.04 (d), 130.67 (d), 131.38 (d), 136.04 (d), 160.23 (d) ppm. MS (CI): *m/z* = 314 (100.0) [M + H$^+$], 316 (99.1) [M + H$^+$].



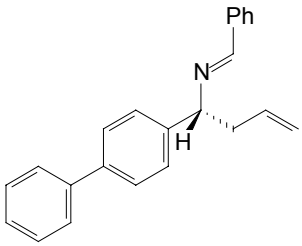
(1*R*)-1-[1,1'-biphenyl]-2-yl-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.30): (red oil, 70 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.64 (t, J = 6.59 Hz, 1H), 4.55 (t, J = 6.59 Hz, 1H), 4.90–4.94 (m, 2H), 5.52–5.66 (m, 1H), 7.20–7.45 (m, 11H), 7.70–7.73 (m, 2H), 7.87 (d, J = 8.06 Hz, 1H), 7.98 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 42.58 (t), 70.40 (d), 116.98 (t), 126.31 (d), 126.86 (d), 127.50 (d), 127.66 (d), 127.95 (d), 128.13 (d), 128.34 (d), 129.40 (d), 129.83 (d), 130.38 (d), 135.26 (d), 136.25 (s), 140.81 (s), 141.04 (s), 141.28 (s), 159.77 (d) ppm. MS (CI): *m/z* = 312 (M + H$^+$).



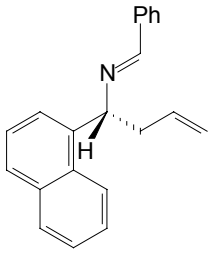
(1*R*)-1-[1,1'-biphenyl]-3-yl-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.31): (red oil, 69 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.81 (t, J = 6.78 Hz, 2H), 4.46 (t, J = 7.69 Hz, 1H), 5.07–5.15 (m, 2H), 5.74–5.88 (m, 1H), 7.37–7.52 (m, 9H), 7.67 (d, J = 7.69 Hz, 2H), 7.76 (s, 1H), 7.81–7.88 (m, 2H), 8.37 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 43.16 (t), 75.34 (d), 117.22 (t), 125.76 (d), 125.84 (d), 125.97 (d), 127.12 (d), 128.24 (d), 128.40 (d), 128.61 (d), 128.74 (d), 130.49 (d), 135.26 (d), 136.14 (s), 141.11 (s), 141.20 (s), 144.28 (s), 160.04 (d) ppm. MS (CI): m/z = 312 [M + H$^+$].



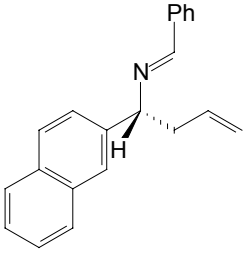
(1*R*)-1-[1,1'-biphenyl]-4-yl-*N*-[(*E*)-phenyl methylidene]-3-buten-1-amine (4.32): (red oil, 79 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.86–3.05 (m, 2H), 4.39 (t, J = 6.8 Hz, 1H), 5.02–5.14 (m, 2H), 5.53–5.69 (m, 1H), 7.06–7.59 (m, 12H), 7.78–7.81 (m, 2H), 8.32 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 43.02 (t), 56.68 (d), 117.20 (t), 126.80 (d), 126.93 (d), 127.04 (d), 127.24 (d), 127.37 (d), 128.03 (d), 128.21 (d), 128.34 (d), 128.75 (d), 131.67 (s), 139.44 (s), 139.94 (s), 154.78 (s), 159.99 (d) ppm. MS (CI): m/z = 312 [M + H$^+$].



(1*R*)-1-(1-naphthyl)-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.39): (green oil, 95 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.89 (t, J = 6.59 Hz, 2H), 5.04–5.13 (m, 2H), 5.19 (t, J = 7.14 Hz, 1H), 5.78–5.92 (m, 1H), 7.39–7.58 (m, 6H), 7.75–7.89 (m, 5H), 8.32 (d, J = 8.42 Hz, 1H), 8.39 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 42.51 (t), 71.22 (d), 117.08 (t), 123.45 (d), 124.65 (d), 125.28 (d), 125.56 (d), 125.80 (d), 127.39 (d), 128.29 (d), 128.45 (d), 128.94 (d), 130.54 (d), 130.64 (s), 133.97 (s), 135.67 (d), 136.30 (s), 139.75 (s), 160.29 (d) ppm. MS (CI): m/z = 286 (M + H$^+$).

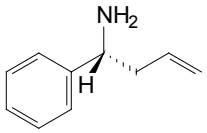


(1*R*)-1-(2-naphthyl)-*N*-[(*E*)-phenylmethylidene]-3-buten-1-amine (4.40): (red oil, 94 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.77 (t, J = 6.96 Hz, 2H), 4.50 (t, J = 6.96 Hz, 1H), 4.98–5.08 (m, 2H), 5.61–5.81 (m, 1H), 7.31–7.48 (m, 5H), 7.60 (d, J = 8.42 Hz, 1H), 7.78–7.84 (m, 6H), 8.34 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 43.05 (t), 75.33 (d), 117.24 (t), 125.51 (d), 125.88 (d), 127.60 (d), 127.86 (d), 128.05 (d), 128.31 (d), 128.49 (d), 130.10 (d), 132.71 (s), 135.34 (d), 136.29 (s), 141.22 (s), 150.95 (s), 160.21 (d) ppm. MS (CI): m/z = 286 (M + H$^+$).

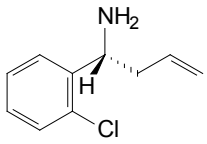


Hydrolysis of the *N*-benzylidene protected homoallylamines 4.23–4.40. *N*-benzylidene **4.23–4.40** (9.94 mmol) was dissolved in a 50 % aqueous THF (100 mL) solution. Hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$, 2.08 gram, 29.8 mmol, 3 equiv.) was added and the reaction mixture was stirred overnight at ambient temperature. The THF was evaporated under reduced pressure and the residue was brought to pH 1 with aqueous HCl (30 %). The aqueous phase was washed once with dichloromethane to remove by-products. The aqueous phase was adjusted to *p*H 10 with aqueous NaOH (33 %) and extracted with dichloromethane. After drying over Na_2SO_4, the solvent was evaporated to furnish the (*R*)-arylbutenylamine as an oily material. If necessary, the 1-aryl-3-butenylamines can be purified by Kugelrohr distillation.

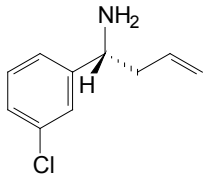
(1*R*)-1-phenyl-3-butenylamine (4.41): (yellow oil, 80 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.57 (brs, 2H), 2.26–2.46 (m, 2H), 3.94 (dd, *J* = 7.87, *J* = 5.31 Hz, 1H), 5.01–5.09 (m, 2H), 5.63–5.77 (m, 1H), 7.29–7.19 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 44.00 (t), 55.19 (d), 117.41 (t), 126.12 (d), 126.77 (d), 128.11 (d), 135.26 (d), 145.65 (s) ppm. MS (CI): *m/z* = 148 [M + H$^+$].

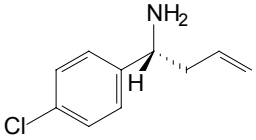


(1*R*)-1-(2-chlorophenyl)-3-butenylamine (4.42): (yellow oil, 75 % yield, >99:1 *er*). $[\alpha]_D^{25}$ = +61.0 (c = 3.44, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.48 (brs, 2H), 2.17–2.27 (m, 1H), 2.42–2.52 (m, 1H), 4.39 (dd, *J* = 8.24, *J* = 4.58 Hz, 1H), 4.97–5.09 (m, 2H), 5.63–5.79 (m, 1H), 7.08 (dt, *J* = 7.69, *J* = 1.09 Hz, 1H), 7.17 (d, *J* = 7.69 Hz, 1H), 7.24 (t, *J* = 8.79 Hz, 1H), 7.44 (dd, *J* = 7.69, *J* = 1.09 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 41.91 (t), 51.04 (d), 117.72 (t), 126.82 (d), 127.03 (d), 127.71 (d), 129.34 (d), 132.55 (s), 134.98 (d), 142.71 (s) ppm. MS (CI): *m/z* = 182 (100.0) [M + H$^+$], 184 (33.1) [M + H$^+$].

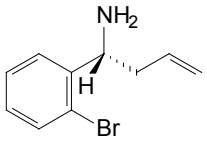


(1*R*)-1-(3-chlorophenyl)-3-butenylamine (4.43): (yellow oil, 58 % yield, >99:1 *er*). $[\alpha]_D^{25}$ = +31.5 (c = 2.98, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.55 (brs, 2H), 2.21–2.42 (m, 2H), 3.91 (dd, *J* = 7.87, *J* = 5.13 Hz, 1H), 5.02–5.08 (m, 2H), 5.59–5.73 (m, 1H), 7.12–7.22 (m, 3H), 7.29 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 43.87 (t), 54.73 (d), 117.85 (d), 124.41 (d), 126.37 (d), 127.01 (d), 129.47 (d), 134.02 (s), 134.72 (d), 147.80 (s) ppm. MS (CI): *m/z* = 182 (100.0) [M + H$^+$], 184 (34.3) [M + H$^+$].

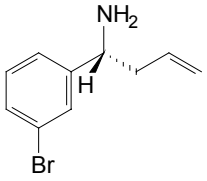




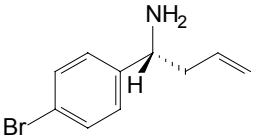
(1*R*)-1-(4-chlorophenyl)-3-butenylamine (4.44): (orange oil, 70 % yield, >99:1 *er*). $[\alpha]_D^{25}$ = +30.0 (c = 2.99, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.59 (brs, 2H), 2.18–2.37 (m, 2H), 3.88 (dd, *J* = 7.69, *J* = 5.50 Hz, 1H), 4.98–5.05 (m, 2H), 5.56–5.70 (m, 1H), 7.16–7.27 (m, 4H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 43.91 (t), 54.51 (d), 117.75 (t), 127.56 (d), 128.24 (d), 132.25 (s), 134.76 (d), 144.00 (s) ppm. MS (CI): *m/z* = 182 (100.0) [M + H$^+$], 184 (32.5) [M + H$^+$].



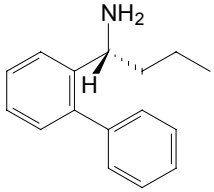
(1*R*)-1-(2-bromophenyl)-3-butenylamine (4.45): (red oil, 65 % yield, >99:1 *er*). $[\alpha]_D^{25}$ = +39.3 (c = 2.40, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.49 (brs, 2H), 2.13–2.23 (m, 1H), 2.42–2.50 (m, 1H), 4.34 (dd, *J* = 8.42, *J* = 4.40 Hz, 1H), 4.97–5.09 (m, 2H), 5.65–5.70 (m, 1H), 7.00 (t, *J* = 7.69 Hz, 1H), 7.22 (t, *J* = 7.69 Hz, 1H), 7.44 (d, *J* = 8.06 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 41.98 (t), 53.41 (d), 117.74 (t), 123.06 (s), 127.24 (d), 127.43 (d), 128.09 (d), 132.59 (d), 134.91 (d), 144.20 (s) ppm. MS (CI): *m/z* = 226 (67.3) [M + H$^+$], 228 (74.0) [M + H$^+$].



(1*R*)-1-(3-bromophenyl)-3-butenylamine (4.46): (yellow oil, 51 % yield, >99:1 *er*). $[\alpha]_D^{25}$ = +29.9 (c = 2.84, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.87 (brs, 2H), 2.12–2.42 (m, 2H), 3.90 (dd, *J* = 7.69, *J* = 5.49 Hz, 1H), 4.97–5.08 (m, 2H), 5.59–5.72 (m, 1H), 7.12 (t, *J* = 7.69 Hz, 1H), 7.20 (d, *J* = 7.69 Hz, 1H), 7.30 (d, *J* = 7.69 Hz, 1H), 7.44 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 43.89 (t), 54.83 (d), 117.75 (t), 118.06 (t), 122.46 (s), 125.00 (d), 129.44 (d), 129.91 (d), 129.99 (d), 134.73 (d), 147.95 (s) ppm. MS (CI): *m/z* = 226 (100.0) [M + H$^+$], 228 (97.4) [M + H$^+$].



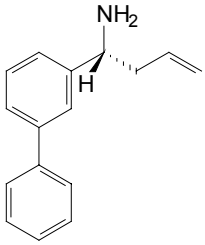
(1*R*)-1-(4-bromophenyl)-3-butenylamine (4.47): (pale yellow oil, 48 % yield, >99:1 *er*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.61 (brs, 2H), 2.12–2.41 (m, 2H), 3.92 (t, *J* = 6.37 Hz, 1H), 5.02–5.08 (m, 2H), 5.59–5.73 (m, 1H), 7.17 (d, *J* = 8.42 Hz, 2H), 7.39 (d, *J* = 8.42 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 44.05 (t), 54.77 (d), 118.01 (t), 120.60 (s), 128.11 (d), 131.43 (d), 134.87 (d), 150.98 (s) ppm. MS (CI): *m/z* = 226 (100.0) [M + H$^+$], 228 (98.0) [M + H$^+$].



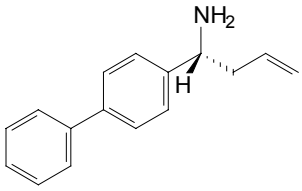
(1*R*)-1-[1,1'-biphenyl]-2-yl-3-butenylamine (4.48): (yellow oil, 57 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.20–2.40 (m + brs, 4H), 3.98 (t, *J* = 4.22 Hz, 1H), 4.94–5.03 (m, 2H), 5.56–5.73 (m, 1H), 7.05–7.34 (m, 9H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 44.52 (t), 55.62 (d), 120.72 (t), 125.25 (d), 126.03 (d), 126.78 (d), 128.86 (d),

130.03 (d), 130.22 (d), 133.33 (d), 135.28 (s), 145.79 (s), 148.22 (s). MS (CI): *m/z* = 224 [M + H^+].

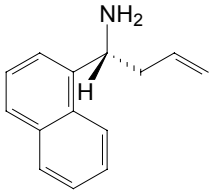
(1*R*)-1-[1,1'-biphenyl]-3-yl-3-butenylamine (4.49): (yellow oil, 45 % yield). $[\alpha]_D^{25}$ = +12.5 (c = 0.98, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.96 (brs, 1H), 2.28–2.47 (m, 2H), 3.99 (t, *J* = 6.41 Hz, 1H), 5.01–5.20 (m, 2H), 5.65–5.78 (m, 1H), 7.24–7.42 (m, 6H), 7.52–7.55 (m, 3H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 44.00 (t), 55.22 (d), 117.51 (t), 124.99 (d), 125.10 (d), 125.57 (d), 126.94 (d), 127.04 (d), 128.50 (d), 128.61 (d), 135.17 (d), 140.96 (s), 141.07 (s), 146.12 (s) ppm. MS (CI): *m/z* = 224 [M + H^+].



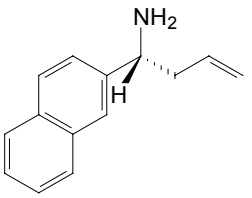
(1*R*)-1-[1,1'-biphenyl]-4-yl-3-butenylamine (4.50): (yellow oil, 49 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.85 (brs, 2H), 2.28–2.51 (m, 1H), 2.81–3.00 (m, 1H), 4.00 (t, *J* = 5.86 Hz, 1H), 4.98–5.13 (m, 2H), 5.50–5.80 (m, 1H), 7.09–7.46 (m, 7H), 7.53 (t, *J* = 7.32 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 40.02 (t), 55.05 (d), 117.77 (t), 126.93 (d), 127.00 (d), 128.09 (d), 128.70 (d), 130.10 (d), 131.14 (s), 135.92 (d), 139.91 (s), 140.86 (s) ppm. MS (CI): *m/z* = 224 [M + H^+].



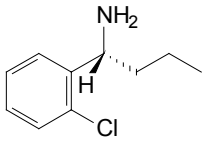
(1*R*)-1-(1-naphthyl)-3-butenylamine (4.51): (yellow oil, 60 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.65 (brs, 2H), 2.38–2.48 (m, 2H), 4.82 (dd, *J* = 7.51, *J* = 3.85 Hz, 1H), 5.10–5.20 (m, 2H), 5.77–5.91 (m, 1H), 7.43–7.52 (m, 3H), 7.63 (d, *J* = 6.96 Hz, 1H), 7.73 (d, *J* = 8.05 Hz, 1H), 7.84 (d, *J* = 7.69 Hz, 1H), 8.11 (d, *J* = 7.69 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 43.00 (t), 50.17 (d), 117.57 (t), 122.35 (d), 122.69 (d), 125.26 (d), 125.38 (d), 125.81 (d), 127.22 (d), 128.85 (d), 130.67 (s), 133.74 (s), 135.46 (d), 141.28 (s) ppm. MS (CI): *m/z* = 198 (M + H^+).



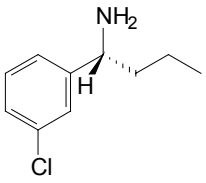
(1*R*)-1-(2-naphthyl)-3-butenylamine (4.52): (yellow oil, 47 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.68 (brs, 2H), 2.35-2.55 (m, 2H), 4.10 (t, *J* = 6.59 Hz, 1H), 5.66–5.80 (m, 2H), 7.38–7.44 (m, 3H), 7.73–7.79 (m, 4H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 43.89 (t), 55.28 (d), 117.58 (t), 124.54 (d), 124.73 (d), 125.39 (d), 125.87 (d), 127.48 (d), 127.66 (d), 127.97 (d), 132.58 (s), 133.28 (s), 135.22 (d), 143.09 (s) ppm. MS (CI): *m/z* = 198 (M + H^+).



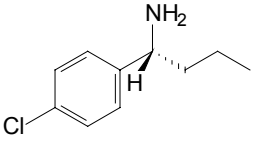
Typical procedure for the catalytic hydrogenation of 1-aryl-3-butenylamines (*R*)-4.41–4.52. The 1-aryl-3-butenylamine **4.41**–**4.52** (15.0 mmol) was dissolved in EtOAc (100 mL), and Pt–C (5 %) (0.6 gram, cat.) was added successively. After two vacuum/H_2 cycles to remove air from the reaction flask, the stirred mixture of the substrate was hydrogenated at ambient pressure of H_2 and room temperature for 1 hour. The catalyst was removed by filtration over Celite. The filtrate was concentrated in vacuo to give the arylbutylamine as an oil.



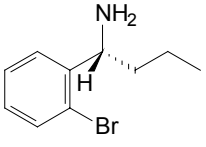
(1*R*)-1-(2-chlorophenyl)butylamine (4.53): (green oil, 91 % yield, >99:1 *er*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.87 (t, J = 7.33 Hz, 3H), 1.21–1.43 (m, 2H), 1.57–1.72 (m, 2H), 1.90 (brs, 2H), 4.34 (t, J = 6.60 Hz, 1H), 7.09 (t, J = 7.69 Hz, 1H), 7.19 (d, J = 7.69 Hz, 1H), 7.25 (t, J = 8.24 Hz, 1H), 7.41 (d, J = 7.30 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 13.71 (q), 19.32 (t), 39.85 (t), 51.37 (d), 126.80 (d), 127.46 (d), 129.21 (d), 132.58 (s), 143.48 (s) ppm. MS (CI): *m/z* = 184 (100.0) [M + H^+], 186 (33.1) [M + H^+].



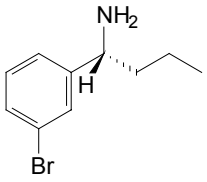
(1*R*)-1-(3-chlorophenyl)butylamine (4.54): (orange oil, >99 % yield, >99:1 *er*). $[\alpha]_D^{25}$ = +24.2 (c = 3.14, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.83 (t, J = 7.33 Hz, 3H), 1.09–1.33 (m, 2H), 1.46–1.61 (m, 2H), 1.65 (brs, 2H), 3.79 (t, J = 6.59 Hz, 1H), 7.09–7.20 (m, 3H), 7.24 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.85 (q), 19.48 (t), 41.61 (t), 55.51 (d), 124.47 (d), 126.41 (d), 126.82 (d), 129.53 (d), 134.08 (s), 148.79 (s) ppm. MS (CI): *m/z* = 184 (100.0) [M + H^+], 186 (33.5) [M + H^+].



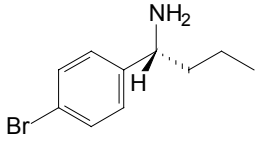
(1*R*)-1-(4-chlorophenyl)butylamine (4.55): (yellow oil, >99 % yield, >99:1 *er*). $[\alpha]_D^{25}$ = +11.2 (c = 6.35, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.83 (t, J = 7.14 Hz, 3H), 1.15–1.32 (m, 2H), 1.49–1.64 (m, 2H), 2.11 (brs, 2H), 3.83 (t, J = 6.77 Hz, 1H), 7.19 (d, J = 8.42 Hz, 2H), 7.23 (d, J = 8.42 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.68 (q), 19.29 (t), 41.41 (t), 55.06 (d), 127.49 (d), 128.14 (d), 132.01 (s), 144.75 (s) ppm. MS (CI): *m/z* = 184 (100.0) [M + H^+], 186 (32.7) [M + H^+].



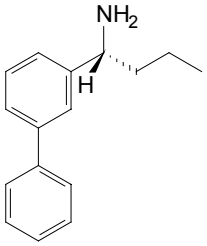
(1*R*)-1-(2-bromophenyl)butylamine (4.56): (dark green oil, 99 % yield, >99:1 *er*). $[\alpha]_D^{25}$ = +17.9 (c = 3.33, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.86 (t, J = 7.33 Hz, 3H), 1.16–1.38 (m, 2H), 1.46–1.70 (m, 2H), 2.00 (brs, 2H), 4.28 (t, J = 6.78 Hz, 1H), 7.00 (dt, J = 7.69, J = 1.46 Hz, 1H), 7.23 (t, J = 7.69 Hz, 1H), 7.39 (dd, J = 7.69, J = 1.46 Hz, 1H), 7.44 (dd, J = 7.69, J = 1.46 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.76 (q), 19.32 (t), 39.91 (t), 53.81 (d), 123.19 (s), 127.03 (d), 127.48 (d), 127.92 (d), 132.51 (d), 144.89 (s) ppm. MS (CI): *m/z* = 228 (63.2) [M + H^+], 230 (61.2) [M + H^+].



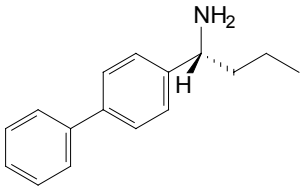
(1*R*)-1-(3-bromophenyl)butylamine (4.57): (orange oil, >99 % yield, >99:1 *er*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.82 (t, J = 7.32 Hz, 3H), 1.08–1.31 (m, 2H), 1.49–1.63 (m, 2H), 2.56 (brs, 2H), 3.78 (t, J = 6.96 Hz), 7.10 (t, J = 7.69 Hz, 1H), 7.15 (d, J = 7.69 Hz, 1H), 7.28 (d, J = 7.69 Hz, 1H), 7.40 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.85 (q), 19.48 (t), 41.61 (t), 55.51 (d), 124.47 (d), 126.41 (d), 126.82 (d), 129.53 (d), 134.08 (s), 148.79 (s) ppm. MS (CI): *m/z* = 228 (100.0) [M + H$^+$], 230 (96.6) [M + H$^+$].



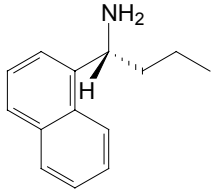
(1*R*)-1-(4-bromophenyl)butylamine (4.58): (yellow oil, 85 % yield, >99:1 *er*). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.81 (t, J = 7.32 Hz, 3H), 1.04–1.33 (m, 2H), 1.43–1.56 (m + brs, 4H), 3.78 (t, J = 6.78 Hz, 1H), 7.15 (d, J = 8.06 Hz, 2H), 7.35 (d, J = 8.06 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.84 (q), 19.44 (t), 41.62 (t), 55.27 (d), 120.23 (s), 128.22 (d), 131.25 (d), 150.85 (s) ppm. MS (CI): *m/z* = 228 (95.8) [M + H$^+$], 230 (100.0) [M + H$^+$].



(1*R*)-1-[1,1'-biphenyl]-3-ylbutylamine (4.59): (pale green oil, 93 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.88 (t, J = 7.33 Hz, 3H), 1.15–1.41 (m, 2H), 1.61–1.73 (m, 2H), 2.14 (brs, 2H), 3.92 (t, J = 6.96 Hz, 1H), 7.25–7.45 (m, 6H), 7.51 (s, 1H), 7.59 (d, J = 6.95 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 11.56 (q), 17.27 (t), 39.27 (t), 53.64 (d), 122.79 (d), 122.82 (d), 123.28 (d), 124.72 (d), 124.78 (d), 126.24 (d), 126.39 (d), 138.77 (s), 138.88 (s), 144.54 (s) ppm. MS (CI): *m/z* = 226 [M + H$^+$].



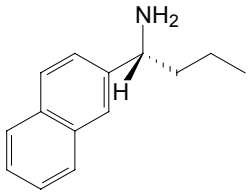
(1*R*)-1-[1,1'-biphenyl]-4-ylbutylamine (4.60): (orange oil, 95 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.82 (t, J = 7.32 Hz, 3H), 1.20–1.41 (m, 2H), 1.55–1.68 (m + brs, 4H), 3.89 (t, J = 6.96 Hz, 1H), 7.27–7.41 (m, 7H), 7.54 (t, J = 8.42 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.77 (q), 19.44 (t), 41.54 (t), 55.36 (d), 126.46 (d), 126.65 (d), 126.77 (d), 128.42 (d), 139.34 (s), 140.60 (s), 145.59 (s) ppm. MS (CI): *m/z* = 226 [M + H$^+$].



(1*R*)-1-(1-naphthyl)butylamine (4.61): (yellow oil, >99 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 0.90 (t, J = 7.33 Hz, 1H), 1.31–1.49 (m, 2H), 1.65–1.89 (m + brs, 4H), 4.73 (t, J = 6.41 Hz, 1H), 7.40–7.49 (m, 3H), 7.57 (d, J = 7.32 Hz, 1H), 7.69 (d, J = 8.05 Hz, 1H), 7.82 (d, J = 7.69 Hz, 1H), 8.10 (d, J = 8.05 Hz, 1H) ppm.

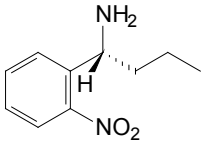
^{13}C-NMR (50MHz, $CDCl_3$) δ = 14.01 (q), 19.86 (t), 40.95 (t), 50.60 (d), 122.24 (d), 122.80 (d), 125.26 (d), 125.48 (d), 125.76 (d), 127.08 (d), 128.85 (d), 130.86 (s), 133.78 (s), 142.2 (s) ppm. MS (CI): *m/z* = 200 ($M + H^+$).

(1*R*)-1-(2-naphthyl)butylamine (4.62): (yellow oil, >99 % yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ = 0.86 (t, *J* = 7.32 Hz, 3H), 1.15–1.39 (m, 2H), 1.42–1.72 (m + brs, 4H), 4.02 (t, *J* = 6.96 Hz, 1H), 7.37–7.42 (m, 3H), 7.69 (s, 1H), 7.75–7.80 (m, 3H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$) δ = 13.82 (q), 19.35 (t), 41.18 (t), 55.80 (d), 124.53 (d), 124.64 (d), 125.26 (d), 125.75 (d), 127.39 (d), 127.52 (d), 127.93 (d), 132.48 (s), 133.19 (s), 143.48 (s) ppm. MS (CI): *m/z* = 200 ($M + H^+$).

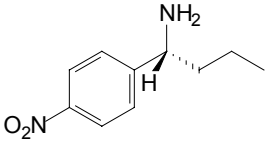


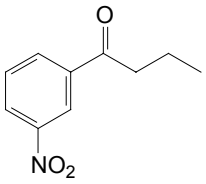
Synthesis of the nitro-substituted 1-phenyl-1-butylamines (*R*)-4.64 and (*R*)-4.65. Enantiomerically pure (*R*)-1-phenyl-1-butylamine **3.64** (35 mmol, 5.22 gram) was cautiously added with continuous stirring during 10 minutes to HNO_3 (30 mL) at –5 °C. An exothermic reaction proceeded, and the temperature was maintained at –5 °C. The reaction was followed by ^{1}H-NMR, and was complete after stirring at –5 °C for 1 hour. The reaction mixture was poured on crushed ice (100 gram) and the *p*H was carefully adjusted to a value of 10 with aqueous NaOH (33 %). The aqueous layer was extracted with dichloromethane and dried over sodium sulphate. Removal of the solvent provided a mixture of (*R*)-**4.64** and (*R*)-**4.65** in a ratio of 22:78 and this mixture of regio-isomers was used without further purification.

(1*R*)-1-(2-nitrophenyl)butylamine (4.64): (yellow oil, 20 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.14 Hz, 3H), 1.14–1.36 (m, 2H), 1.55–1.84 (m, 2H), 1.96 (brs, 2H), 3.99 (t, *J* = 6.78 Hz, 1H), 7.40–7.63 (m, 2H), 8.03–8.26 (m, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.75 (q), 19.30 (t), 41.40 (t), 55.28 (d), 121.29 (d), 121.86 (d), 129.21 (d), 132.74 (d), 146.75 (s), 148.20 (s), 152.97 (s) ppm. MS (CI): *m/z* = 195 [$M + H^+$].

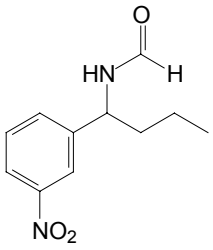


(1*R*)-1-(4-nitrophenyl)butylamine (4.65): (yellow oil, 75 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.14 Hz, 3H), 1.17–1.34 (m, 2H), 1.47 (brs, 2H), 1.51–1.63 (m, 2H), 3.98 (t, *J* = 6.78 Hz, 1H), 7.44 (d, *J* = 8.79 Hz, 2H), 8.12 (t, *J* = 8.79 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.79 (q), 19.34 (t), 41.66 (t), 55.40 (d), 123.51 (d), 127.12 (d), 146.15 (s), 154.28 (s) ppm. MS (CI): *m/z* = 195 [$M + H^+$].



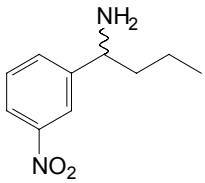


***Meta*-nitrobutyrophenone (4.67):**[14] Commercially available butyrophenone **4.66** (169 mmol, 25.0 gram) was cautiously added with continuous stirring during 30 minutes to HNO_3 (150 mL) at –5 °C. An exothermic reaction proceeded, and the temperature was maintained at –5 °C. The reaction was followed by ^{1}H-NMR, and was complete after stirring at –5 °C for 4 hours. The reaction mixture was poured on crushed ice (500 gram), the crude *meta*-nitro compound precipitated as a yellow curdled solid. The yellow solid was removed by filtration under suction and subsequently dissolved in diethyl ether (200 mL) and dried over sodium sulphate. After filtration and removal of the ether an yellow oil was obtained, from which the crude *m*-nitro compound separated on standing as yellow plates. After removal of the oil, the yellow plates were recrystallized once from abs. alcohol. Pure **4.67** was obtained as pale yellow plates (92.9 mmol, 18.0 gram, 55 % yield). m.p. 60.4–60.6 °C; lit.[14a] 61°C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.91 (t, J = 7.33 Hz, 3H), 1.63–1.75 (m, 2H), 2.92 (t, J = 7.14 Hz, 2H), 7.59 (dt, J = 8.06 Hz, 1H), 8.19 (d, J = 7.69 Hz, 1H), 8.28 (d, J = 8.06 Hz, 1H), 8.63 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.56 (q), 17.23 (t), 40.49 (t), 122.67 (d), 126.99 (d), 129.75 (d), 138.07 (s), 139.46 (d), 148.24 (s), 197.85 (s) ppm. Anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17 %; H, 5.74 %; N, 7.25 %. Found: C, 62.15 %; H, 5.68 %; N, 7.32 %. MS (EI): m/z = 193 [M^+].

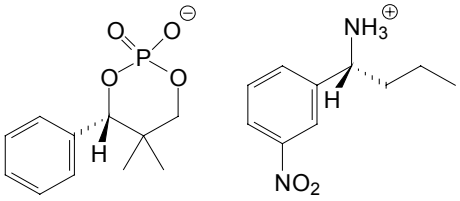


(±)-1-(3-Nitrophenyl)butylformamide (4.68): A mixture of *m*-nitrobutyrophenone **4.67** (129 mmol, 25.0 gram), formamide (77 mL) and formic acid (35 mL) was heated to reflux. The mixture was refluxed for several hours until the reaction was complete (followed by ^{1}H-NMR). After cooling to ambient temperature, 200 mL of water was added and the mixture was extracted with diethylether (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to furnish a red oil (129 mmol, 28.7 gram, >99 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.80 (t, J = 7.32 Hz, 3H), 1.11–1.36 (m, 2H), 1.58–1.75 (m, 2H), 4.98 (dd, J = 15.01, J = 7.69 Hz, 1H), 7.31 (brs, 1H), 7.38 (t, J = 8.06 Hz, 1H), 7.54 (d, J = 7.69 Hz, 1H), 7.97 (d, J = 8.06 Hz, 1H), 8.07 (s, 1H), 8.09 (s, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.35 (q), 19.05 (t), 37.85 (t), 51.78 (d), 120.97 (d), 122.24 (d), 129.50 (d), 133.06 (d), 144.18 (s), 148.18 (s), 162.19 (d) ppm. MS (CI): m/z = 223 [M + H^+].

(±)-1-(3-Nitrophenyl)-1-butylamine (4.69): A mixture of (±)–**4.68** (129 mmol, 28.7 gram) and 100 mL aqueous HCl (30 %) was refluxed overnight. After cooling to ambient temperature, 200 mL of water was added. The reaction mixture was carefully adjusted to pH 10 with aqueous NaOH (33 %) and extracted with diethylether (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to furnish a red oil.



Second Generation Dutch Resolution of (±)-4.69: To a solution of the racemic substrate (80.00 mmol, 15.54 gram) in 160.0 mL 2-butanone and 80.0 mL of water was added one equivalent of the mixture of resolving agents (consisting of 72 mmol (+)-**4.70** and 8 mmol of (+)-**4.73**). The mixture was heated until a clear solution was obtained. While stirring, the solution was allowed to cool to room temperature overnight. The salt was removed by filtration under suction and washed with a little *i*-propanol. The salt obtained was recrystallized once from *i*-propanol/H_2O (2:1). ^{1}H-NMR (300MHz, [D$_6$]DMSO): δ = 0.61 (s, 3H), 0.78 (t, J = 7.20 Hz, 3H), 0.83 (s, 3H), 1.04–1.27 (m, 2H), 1.76–2.01 (m, 2H), 3.23 (dd, $^3J_{P\text{-}H}$ = 23.07, $^2J_{AB}$ = 10.61 Hz, 1H), 3.99 (d, $^3J_{P\text{-}H}$ = 10.26 Hz, 1H), 4.38 (dd, J = 8.61, J = 5.68 Hz, 1H), 5.00 (d, $^3J_{P\text{-}H}$ = 2.68 Hz, 1H), 7.24–7.35 (m, 5H), 7.70 (t, J = 8.05 Hz, 1H), 8.00 (d, J = 7.69 Hz, 1H), 8.23 (d, J = 8.42 Hz, 1H), 8.45 (s, 1H), 8.81 (brs, 3H, NH_3^+). ^{13}C-NMR (50MHz, [D$_6$]DMSO) δ = 12.35 (q), 16.32 (q), 17.26 (t), 19.92 (q), 34.24 (s, $^3J_{C\text{-}P}$ = 2.67 Hz), 35.15 (t), 52.27 (d), 74.36 (t, $^2J_{C\text{-}P}$ = 4.96 Hz), 82.43 (d), 121.43 (d), 122.22 (d), 126.16 (d), 126.24 (d), 126.35 (d), 129.19 (d), 133.30 (d), 137.88 (s, $^3J_{C\text{-}P}$ = 11.50 Hz), 139.62 (s), 146.83 (s). ^{31}P-NMR (81MHz, [D$_6$]DMSO): δ = –5.08. Anal. calcd for $C_{10}H_{14}N_2O_2 \cdot C_{11}H_{15}O_4P$: C, 57.79 %; H, 6.70 %; N, 6.42 %. Found: C, 57.57 %; H, 6.90 %; N, 6.31 %.



The less soluble salt was shown to contain (*R*)–**4.69** of >99 % *ee* by HPLC analysis.[10] The purified salt was treated with 6 M NaOH solution to liberate the free amine (*R*)–**4.69** of >99 % *ee* in 24 % yield starting from (±)–**4.69**. $[\alpha]_D^{25}$ = –5.4 (c = 2.15, $CHCl_3$). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 0.77 (t, J = 7.32 Hz, 3H), 1.04–1.29 (m, 2H), 1.47–1.58 (m + brs, 4H), 3.91 (t, J = 6.78 Hz, 1H), 7.35 (t, J = 7.69 Hz, 1H), 7.55 (d, J = 7.69 Hz, 1H), 7.92 (d, J = 8.06 Hz, 1H), 8.06-8.09 (m, 1H) ppm. ^{13}C-NMR (50MHz,$CDCl_3$): δ = 13.67 (t), 19.23 (q), 41.57 (t), 55.16 (d), 121.21 (d), 121.58 (d), 129.01 (d), 132.61 (d), 148.06 (s), 148.76 (s) ppm. MS (CI): *m/z* = 195 [M + H$^+$].

X-ray crystallographic data of (*S*)-**4.70**/(*R*)-**4.69**[18]

Formula	$[C_{11}H_{14}O_4P]^-.[C_{10}H_{15}N_2O_2]^+$
Mw ($g \cdot mol^{-1}$)	436.43
Crystal dimension (mm)	0.50 × 0.16 × 0.15
Color	colorless
Habit	needles (bunchlike)
Crystal system	orthorhombic
Space group, no.	$P2_12_12_1$
a (Å)	6.0128 (4)
b (Å)	18.562 (1)
c (Å)	19.190 (1)
β (°)	
V (Å ^{3})	2141.8 (2)
Z	4
ρ ($g \cdot cm^{-3}$)	1.353
T (K)	100 (1)
μ (cm^{-1})	1.69
number of reflections	5278
number of refined parameters	387
final agreement factors:	
$wR(F^2)$	0.0782
$R(F)$	0.0307
GooF	1.064

4.8 References

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[10] Conditions for HPLC Analysis:

HPLC column	Conditions	Ret. Times (min.)
Diacel	aqueous $HClO_4$,	51.7 (*R*)
Crownpack CR(–)	pH = 2.0	57.2 (*S*)
Analytic column 150 × 4.0 mm	1.0 mL·min^{-1}	(at λ = 200 nm)

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[17] IUPAC-names of the family of cyclic phosphoric acids: (*S*)-(+)-Phencyphos (**4.65**): (*S*)-(+)-2-hydroxy-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-di-oxa phosphorinane, (*R*)-(+)-Chlocyphos (**4.66**): (*R*)-(+)-4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane, (*S*)-(+)-Anicyphos (**4.67**): (*S*)-(+)-2-hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-2-oxo-1,3,2-dioxa phosphorinane, (*S*)-(+)-Nitrocyphos (**4.68**): (*S*)-(+)-2-hydroxy-4-(2-nitro)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane. *Note that all (+)-enantiomers are homochiral; because of CIP-rules for the various aromatic substituents, the priority may change from (S) to (R).*

[18] CCDC-200249 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: (internat.) + 44-1223/336-033; Email: deposit@ccdc.cam.ac.uk].

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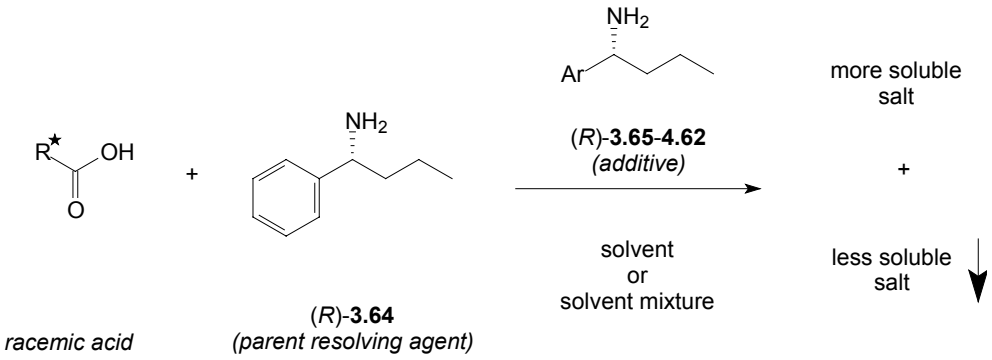
Chapter 5
Families based on 1-Arylbutylamines in Second Generation Dutch Resolution Experiments

In this chapter second generation Dutch Resolution experiments with a family based on 1-arylbutylamines are described. Mandelic acid, 2-phenylbutyric acid, N-acetylleucine and Chlocyphos were chosen as candidates for (Dutch) resolution attempts. Furthermore, experimental conditions and apparatus that are necessary to achieve reproducible results are specified.

5.1 Introduction

The second generation Dutch Resolution protocol[†] is based on the use of non-equivalent amounts of two structurally closely related resolving agents (family members). The resolving agent present in largest amount is called the "parent resolving agent" and the other component present in smaller amount (~10 mol %) is the "additive".[1] Typically, the additive is a poorly or non-incorporated family member.

The diastereoselective formation of (*R*)-PGA protected homoallylamines described in Chapter 3 of this thesis gives easy access to enantiomerically pure 1-arylbutylamines. In theory, each of these amines could be used as a (new) resolving agent. Mixtures of these amines would provide a novel system based on a family of enantiopure (*R*)-1-arylbutylamines instead of 1-arylethylamines (as in the original work by Nieuwenhuijzen).[1a,b] In the system chosen for investigation, the parent resolving agent is the unsubstituted (*R*)-1-phenylbutylamine **3.64** and the additive is typically 10 mol % of **3.65**–**4.62** (Scheme 5.1).



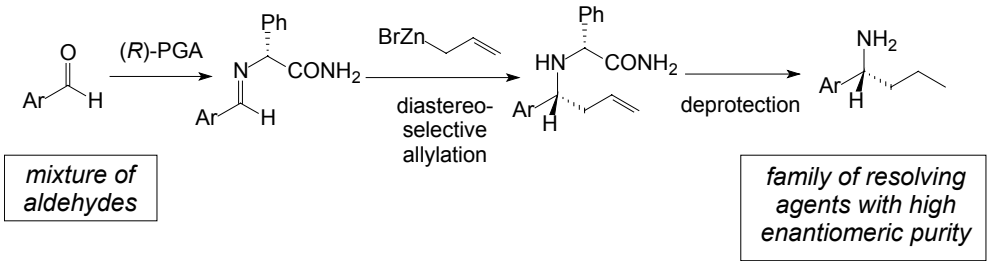
Scheme 5.1 *New possible system for Dutch Resolution experiments based on **3.64**.*

In advance of performing experiments one could imagine both advantages and disadvantages:

- Instead of preparing each family member individually, combinatorial approaches might also be applied by starting from a mixture of aldehydes. In a single step, a mixture of

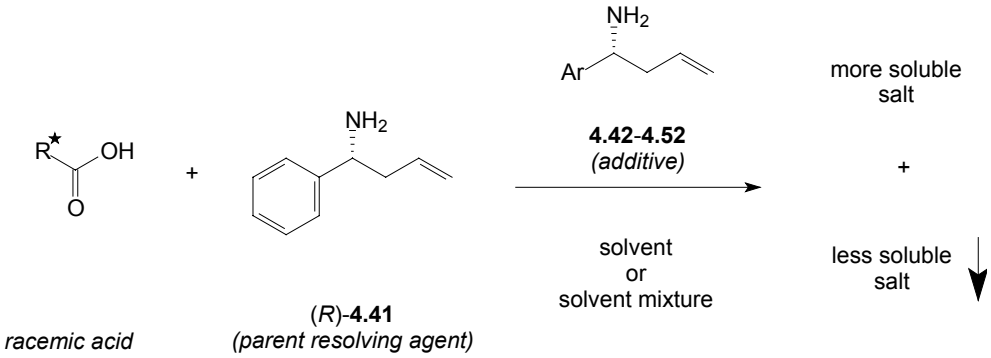
[†] *A more detailed description of the second generation Dutch Resolution protocol can be found in Chapter 1.5.2.*

imines could be prepared by stirring the mixture of aldehydes with (*R*)-PGA. After addition of allylzinc bromide to the crude mixture and subsequent removal of the chiral auxiliary a family of butylamines with high enantiomeric purity would be obtained (Scheme 5.2).



Scheme 5.2 *Facile combinatorial preparation of families of resolving agents based on arylbutylamines.*

- A variation could be based on the non-reductive protocol described in Chapter 4 of this thesis. This would give access to a family based on unsaturated 1-arylbutenylamines (Scheme 5.3). Second generation Dutch Resolution experiments based on this potential new family have not been performed, but are certainly worth investigating.

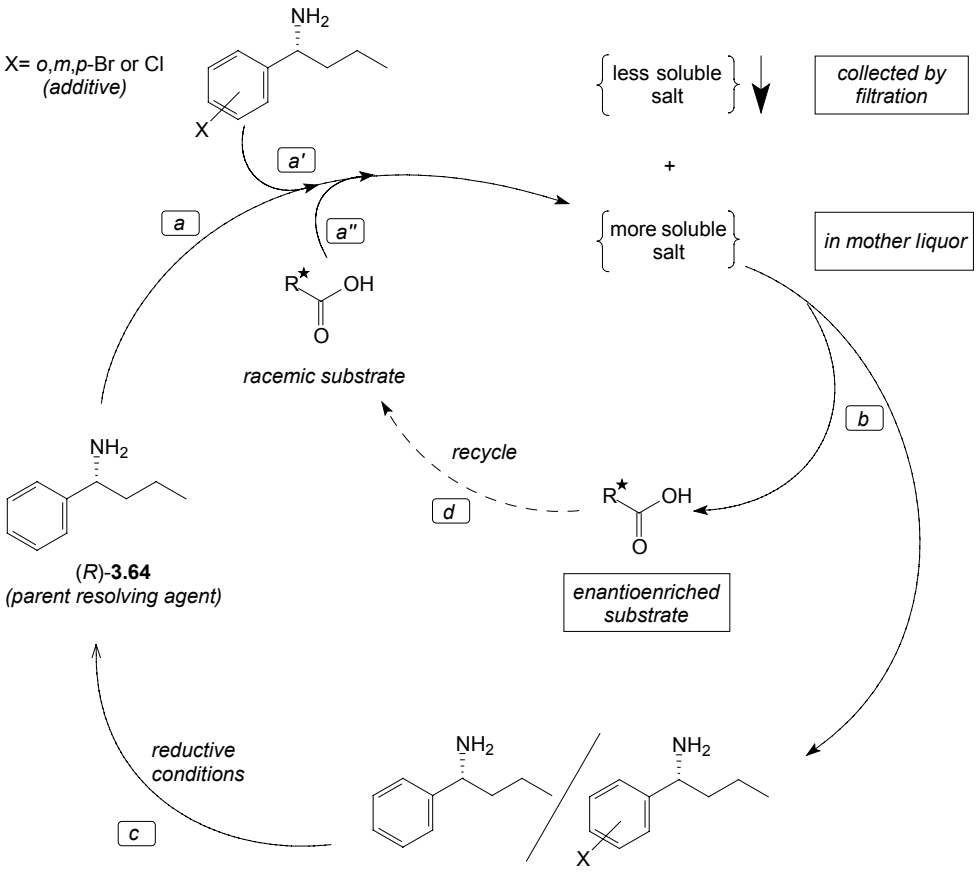


Scheme 5.3 *Another possible system for Dutch Resolution experiments based on unsaturated **4.41**.*

- If a system could be developed in which the parent resolving agent is the unsubstituted phenylbutylamine **3.64**, and one of the chloro- or bromo-substituted family members is

the additive (or a mixture of them), an easy recycling step of the resolving agents would in principle be possible, as illustrated in Scheme 5.4.

If, after salt formation, the nucleation inhibitor is not incorporated in the salt (Scheme 5.4, step *a*), the chloro- or bromo-components can be found in the mother liquor. After separation of the resolving agents and the substrate to be resolved (step *b*) by a simple acid-base extraction, the mixture containing the halo- and unsubstituted family members could be easily recycled (by dehalogenation) into pure parent resolving agent **3.64** using mild reductive conditions (step *c*). Most ideal would be if the substrate of interest could be racemized after step *b* and recycled (step *d*). This way high yields of the enantio-enriched acid could be reached.



Scheme 5.4 *Possible use of halo-substituted nucleation inhibitors and subsequent conversion to parent resolving agent.*[1b]

One must realize, however, that such a scheme is practical only if the halo-substituted additives are (preferably non-incorporated) nucleation inhibitors.

- A complication is the need for fast and accurate analysis of the precipitated salts. Determination of the amount of additive that is incorporated in the salt by ^{1}H-NMR can only be performed in the cases where the additives give rise to a particular signal that is shifted compared to the signal of the parent resolving agent, or additives that give rise to an extra signal. Examples of the latter are the methyl-substituted additives **3.65**–**3.66** (they give rise to a characteristic singlet between $\delta \sim 2.25$–2.31 ppm in ^{1}H-NMR spectra of the salts) and the methoxy-substituted additives **3.67**–**3.70** (a characteristic singlet between $\delta \sim 3.68$–3.76 ppm). By comparing the ratio of the integrals of the signals, the composition of each salt can be determined. In all the other cases, other techniques like HPLC or GC have to be applied and have to be checked for every additive independently. This time-consuming process hampers the quick analysis necessary in every screening process.

5.2 Performing Resolution Experiments

In order to screen potential nucleation inhibitors additives for the system of interest, a method that provides reproducible results is necessary. These preliminary tests are typically conducted on a 1–2 mmol scale. In a nutshell, these experiments based on acid-base interactions consist of a few simple steps (Figure 5.1*a*–*c*).

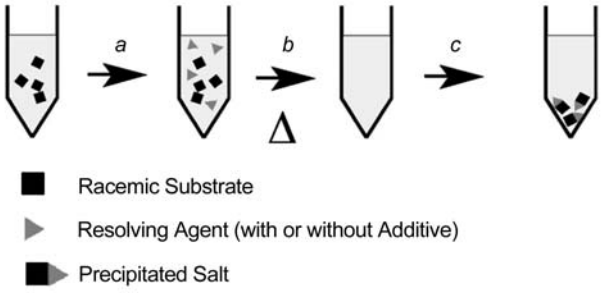


Figure 5.1 *Carrying out a resolution experiment.*

In a general procedure, one mol equivalent of the resolving agent (mixture) was added to a solution of the racemic substrate to be resolved, with or without additive (Figure 5.1*a*). As indicated in Figure 5.1*b*, the resulting mixture is subsequently heated to reflux until a clear solution was obtained (if a clear solution cannot be obtained, more solvent was added) and the mixture is allowed to cool gradually to 20 °C (Figure 5.1*c*). To achieve reproducibility, the gradual cooling is implemented in a (programmable) Varian thermostatted bath (Figure

5.2a). In all experiments, the ramp rate in the cooling process was set to 10 °C per hour. Reproducibilities are exceptionally good and all values reported are mean values from at least three experiments; the experimentally determined error limit of the S-factor is ±5 %.

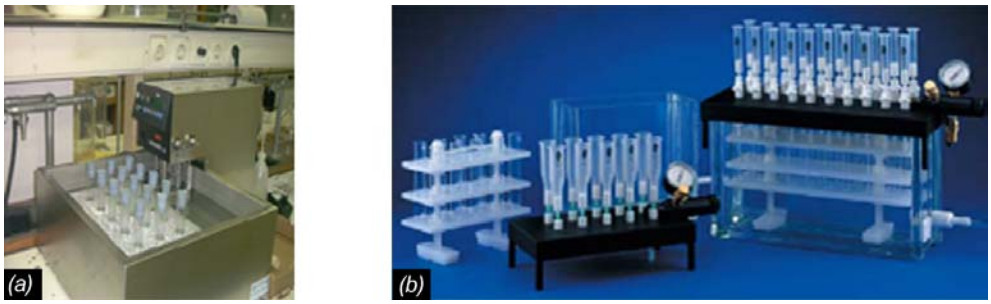
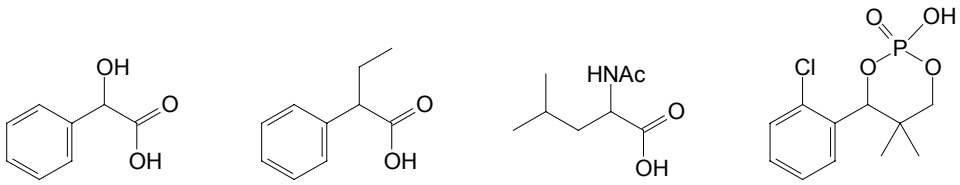


Figure 5.2a and b *Photograph of (a) the Varian thermostatted programmable bath, and (b) the Vacmaster®-10 and 20.*

If a salt precipitates after cooling (so-called 'first (isolated) salt'), it is collected by filtration, dried and analyzed.[2] The collection by filtration was performed on a Vacmaster®-20, which is shown in Figure 5.2b. The VacMaster®-20 can process up to 20 samples simultaneously and the mother liquor is collected in test tubes that are placed in a rack inside.

The following racemic acids were tested in the second generation Dutch Resolution with families based on arylbutylamines; mandelic acid (**5.1**), 2-phenylbutyric acid (**5.2**), *N*-acetylleucine (**5.3**) and Chlocyphos (**5.4**) (Figure 5.3).



5.1 **5.2** **5.3** **5.4**

Figure 5.3 *Racemic substrates tested in second generation Dutch Resolution experiments with families based on arylbutylamines.*

5.3 Results and Discussions

5.3.1 Mandelic Acid

Mandelic acid has been used in medicine for many years as a urinary antiseptic.[3] Recently, mandelic acid has been studied extensively for its possible application in the field of dermatology.

Figure 5.4

With the same conditions used as in the original protocol with mandelic acid as reported by Nieuwenhuijzen,[1] and (*R*)-1-phenyl*butyl*amine **3.64** as the parent resolving agent instead of 1-phenyl*ethyl*amine, no salts precipitated. Generally, when salts are not obtained, one should screen different solvents and/or use higher concentrations. In all solvents screened (*i*-propanol, methanol, 2-butanone, and more apolar solvents such as ethyl acetate and toluene) no salts precipitated. When higher concentrations were used of both mandelic acid **5.1** and parent resolving agent **3.64** (in absence or presence of additive)**,** gel-like materials were obtained (Figure 5.4).

5.3.2 2-Phenylbutyric Acid

2-Phenylbutyric acid is an important intermediate in the synthesis of pharmaceuticals (*e.g.* Indobufen, Pheneturide and Tamoxifen Citrate).[4–6] In the resolution with 1-phenylbutylamine **3.64**, a salt enriched in the less soluble (*S*,*R*)-diastereomer precipitates. The results of the second generation Dutch Resolution experiments are represented in Table 5.1.

In the absence of additive, the resolution of (±)-**5.2** with (*R*)-**3.64** delivered a first salt with a diastereomeric excess (*de*) of 52 % and resolution efficiency (S-factor)[7] of 0.16 (Table 5.1, entry 1). When 10 mol % of (*R*)-**3.64** is replaced by one of the family members **3.65**–**4.62** no significant enhancement in the resolution efficiency was observed. Either both the yield and the *de* remain more or less the same or the *de* values increase a little while the yields decrease to the same extent. In two cases, there is a remarkable increase in *de* of the first isolated salts (entries 10 and 17), but at the same time the yield drops dramatically resulting in an overall moderate S-factor comparable to the blank reaction. On addition of 10 mol % *meta*- or *para*-phenyl-substituted phenylbutylamine (entries 18 and 19) no salts precipitated after a reasonable waiting period (< 1 week).

Table 5.1 *Second generation Dutch Resolution of* ***5.2*** *with* ***3.64*** *in the absence and presence of 10 mol % of an additive.*

Entry	Additive		Yield (%)[a]	*de* (%)[b]	S Factor[c]
	Ar	1-Arylbutylamine			
1	No additive	–	15	52	0.16
2	*o*-Me C_6H_4	**3.65**	23	47	0.22
3	*m*-Me C_6H_4	**3.66**	19	45	0.17
4	*p*-Me C_6H_4	**3.67**	12	60	0.14
5	*o*-OMe C_6H_4	**3.68**	20	36	0.14
6	*m*-OMe C_6H_4	**3.69**	10	64	0.13
7	*p*-OMe C_6H_4	**3.70**	4	66	0.05
8	*o*-F C_6H_4	**3.71**	27	32	0.17
9	*m*-F C_6H_4	**3.72**	6	64	0.08
10	*p*-F C_6H_4	**3.73**	11	74	0.16
11	*o*-Cl C_6H_4	**4.53**	18	42	0.15
12	*m*-Cl C_6H_4	**4.54**	43	15	0.13
13	*p*-Cl C_6H_4	**4.55**	11	67	0.15
14	*o*-Br C_6H_4	**4.56**	16	55	0.18
15	*m*-Br C_6H_4	**4.57**	20	63	0.25
16	*p*-Br C_6H_4	**4.58**	6	61	0.07
17	*o*-Ph C_6H_4	**3.74**	14	83	0.23
18	*m*-Ph C_6H_4	**4.59**	*no salts precipitate*		
19	*p*-Ph C_6H_4	**4.60**	*no salts precipitate*		
20	*o*:*p*-NO_2 C_6H_4	**4.63**:**4.64** (22:78)	6	10	0.01

Entry	Additive		Yield	*de*	S
	Ar	1-Arylbutylamine	(%)[a]	(%)[b]	Factor[c]
21	*m*-NO_2 C_6H_4	**4.68**	18	65	0.23
22	*o*-OH C_6H_4	**3.79**	8	53	0.08
23	1-naphthyl	**4.61**	13	34	0.09
24	2-naphthyl	**4.62**	14	65	0.18

Concentration = 0.57 mmol·mL^{-1} in *i*-propanol. [a] Isolated yield of the first salts. [b] *de* of the first isolated salts.[8] [c] S = 2 × yield × *de*.[7]

5.3.3 *N*-Acetylleucine

In the literature, the resolution of racemic **3.64** with (*S*)-(–)-*N*-acetylleucine **5.3** was reported by Yamamoto and co-workers.[9] Although in this article only the yield and the optical purity after four recrystallization steps from methanol were given, it was clear that **3.64** and **5.4** formed diastereomeric salts. According to the principle of reciprocal resolutions, if a racemic amine can be resolved by an optically active acid, it is frequently (but not always) the case that the racemic acid itself can be resolved by the optically active amine.[10] The results of the second generation Dutch Resolution experiments on the resolution of **5.3** are presented in Table 5.2.

Table 5.2 *Second generation Dutch Resolution of **5.3** with **3.64** in the absence and presence of 10 mol % of an additive.*

Entry	Additive		Yield	*de*	S
	Ar	1-Arylbutylamine	(%)[a]	(%)[b]	Factor[c]
1	No additive	–	13	79	0.21
2	*o*-Me C_6H_4	**3.65**	14	81	0.23
3	*m*-Me C_6H_4	**3.66**	21	60	0.25
4	*p*-Me C_6H_4	**3.67**	16	72	0.23
5	*o*-OMe C_6H_4	**3.68**	16	55	0.18
6	*m*-OMe C_6H_4	**3.69**	4	78	0.06

Entry	Additive		Yield	*de*	S
	Ar	1-Arylbutylamine	(%)[a]	(%)[b]	Factor[c]
7	*p*-OMe C_6H_4	**3.70**	31	72	0.45
8	*o*-F C_6H_4	**3.71**	18	42	0.15
9	*m*-F C_6H_4	**3.72**	21	80	0.34
10	*p*-F C_6H_4	**3.73**	*no salts precipitate*		
11	*o*-Cl C_6H_4	**4.53**	10	82	0.16
12	*m*-Cl C_6H_4	**4.54**	4	78	0.06
13	*p*-Cl C_6H_4	**4.55**	6	71	0.09
14	*o*-Br C_6H_4	**4.56**	19	63	0.24
15	*m*-Br C_6H_4	**4.57**	*no salts precipitate*		
16	*p*-Br C_6H_4	**4.58**	15	77	0.23
17	*o*-Ph C_6H_4	**3.74**	8	53	0.08
18	*m*-Ph C_6H_4	**4.59**	8	60	0.10
19	*p*-Ph C_6H_4	**4.60**	8	81	0.13
20	*o*:*p*-NO_2 C_6H_4	**4.63**:**4.64** (22:78)	*no salts precipitate*		
21	*m*-NO_2 C_6H_4	**4.68**	*no salts precipitate*		
22	*o*-OH C_6H_4	**3.79**	*no salts precipitate*		
23	1-naphthyl	**4.61**	*no salts precipitate*		
24	2-naphthyl	**4.62**	*no salts precipitate*		

Concentration = 0.50 mmol·mL^{-1} in *i*-propanol:H_2O (7:2). [a] Isolated yield of the first salts. [b] *de* of the first isolated salts.[8] [c] S = 2 × yield × *de*.

In the absence of additive, the resolution of (±)-**5.3** with (*R*)-**3.64** delivered a first salt with an encouraging *de* of 79 % but low yield of only 13 % resulting in a modest resolution efficiency of 0.21 (Table 5.2, entry 1). In most cases studied there is no increase in

resolution efficiency in the presence of an additive. Remarkable is the addition of 10 mol % of the *meta*-methoxy- and *meta*-fluoro family members (entries 7 and 9). Both cases resulted in an improvement of the yield, without substantial change in *de*. This effect is poorly understood. One might speculate that we are observing here the effects of *nucleation promotors*.

5.3.4 Chlocyphos

One of the family members of the P-mix, the family of the 'designer resolving agents' first reported by ten Hoeve *et al*.[11] is the chloro-substituted cyclic phosphoric acid **5.4** (Chlocyphos). Attempts to resolve **5.4** with (*R*)-**3.64** with or without additives were not especially encouraging. Only those cases in which salts precipitated are reported in Table 5.3. The results are quite unambiguous; either the additive shows no effect on either yield or *de* of the first isolated salts, or in the presence of an additive no salts precipitated at all. The latter observation could mean that there is a clear nucleation inhibitory effect present but that the nucleation of both diastereomeric salts is hampered. It could be that the additives in Table 5.3 enlarge the metastable zone width only to a small extent and that higher collection temperatures are necessary. In both cases determination of the crystallization behaviour as a function of the temperature might be worth investigating (see also Chapter 6.2.1 and 6.2.3.).

Table 5.3 *Second generation Dutch Resolution of **5.4** with **3.64** in the absence and presence of 10 mol % of an additive.*

Entry	Additive		Yield (%)[a]	*de* (%)[b]	S Factor[c]
	Ar	1-Arylbutylamine			
1	No additive	–	35	5	0.03
2	*p*-Me C_6H_4	**3.66**	36	6	0.05
3	*o*-Cl C_6H_4	**4.53**	35	5	0.04
4	*m*-Cl C_6H_4	**4.54**	35	4	0.03
5	*p*-Cl C_6H_4	**4.55**	36	5	0.03
6	*m*-Ph C_6H_4	**4.59**	33	6	0.04
7	1-naphthyl	**4.61**	36	7	0.05
8	2-naphthyl	**4.62**	35	6	0.05

Concentration = 0.50 mmol·mL^{-1} *i*-propanol:H_2O (1:1). [a] Isolated yield of the first salts. [b] *de* of the first isolated salts.[8] [c] S = 2 × yield × *de*.

5.4 Conclusions

Second generation Dutch resolution experiments based on 1-arylbutylamines as described in this chapter were not too successful under the conditions examined. Possibly, 1-phenylbutylamine **3.64** is not a suitable resolving agent for the substrates studied. Among other possibilities are the following cases:

- Both the yield and the *de* of the first isolated salts stay more or less the same. Either the additive does not induce delayed crystallization or the nucleation temperature is not lowered enough. In these experiments the salts were always collected at a temperature of 20 °C, therefore it could be that both the more soluble and the less soluble diastereomeric salts were fully crystallized. Either determining the crystallization behaviour as a function of temperature (see also Chapter 6.2.1 and Chapter 6.2.1) could give clarification on this point.
- In other cases the yield increases while the *de* drops or remains essentially constant. A plausible explanation could be *promotion* of nucleation of the *less* soluble diastereomeric salt.[12]
- No salts precipitate after a reasonable waiting period. Either, the substrate does not form salts with 3.64 or the additive inhibits the growth of the more soluble as well as the growth of the less soluble diastereomeric salt. In the latter case, lowering the collection temperature might be necessary.

These experiments do not lead to unambiguous conclusions with regard to the relationship of the structure of the additive and the influence on the resolution efficiency. Furthermore, determination of the ratio parent resolving agent/additive in the precipitated salts is hampered by the fact that analysis by ^{1}H-NMR is not possible in most cases.

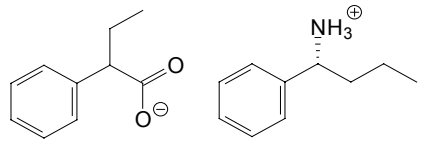
5.5 Experimental Section

General information: For general remarks concerning all experimental details see experimental section in Chapter 3.

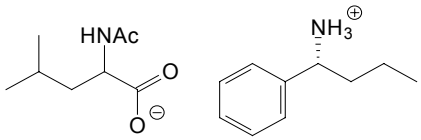
General procedure for the small scale second generation Dutch resolution experiments: In a Kimble reactor tube (dimensions Ø 25 × 150 mm), provided with a cylindrical PTFE magnetic stirring bar (10 × 6 mm), a solution of the racemic substrate (2.00 mmol) in the appropriate solvent(s) was introduced. Subsequently, one equivalent of the mixture of resolving agents (consisting of 1.80 mmol of the parent resolving agent and 0.20 mmol of the additive) was added. The mixture was heated until a clear solution was obtained. After the reactor tube was sealed with a rubber stopper, it was placed in the Varian thermostatted bath and mechanically stirred at 78 °C for 30 minutes. The tubes were gradually cooled to 20 °C with a ramp rate of –10 °C·h^{-1} and stirred at that temperature for 12 h. If a precipite was formed, this was removed by filtration under suction using the

Vacmaster, washed with 2.0 mL of solvent and dried. The precipitated material was analyzed by ^{1}H-NMR. For HPLC determination, the substrate was liberated from the salt by acid-base extraction. To ensure accurate *ee* determination (which corresponds to the *de* value of the salts) racemic mixtures are always measured. The conditions for HPLC analysis for each substrate are given on page 144 from this experimental section.

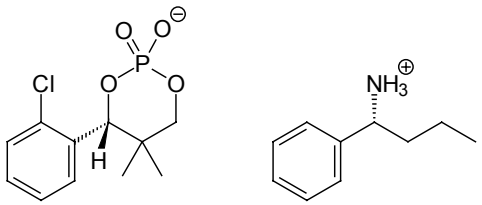
Less soluble salt of 3.65/5.2: ^{1}H-NMR (200MHz, [D$_6$]DMSO): δ = 0.79–0.86 (m, 6H), 1.09–1.29 (m, 2H), 1.49–1.66 (m, 3H), 1.91–2.00 (m, 1H), 3.29 (t, J = 7.50 Hz, 1H), 3.90 (t, J = 6.96 Hz, 1H), 4.71 (brs, 3H, NH_3^+), 7.22–7.37 (m, 10H) ppm. ^{13}C-NMR (50MHz, [D$_6$]DMSO) δ = 12.43 (q), 13.67 (q), 18.74 (t), 26.88 (t), 39.92 (t), 54.56 (d), 54.92 (d), 125.96 (d), 126.86 (d), 127.16 (d), 127.79 (d), 127.91 (d), 128.22 (d), 141.99 (s), 148.48 (s), 175.82 (s) ppm.



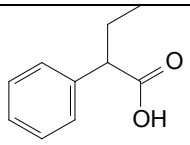
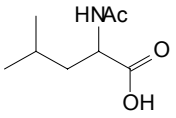
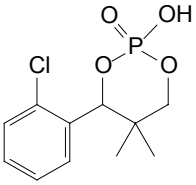
Less soluble salt of 3.65/5.3: ^{1}H-NMR (400MHz, [D$_6$]DMSO): δ = 0.74–0.81 (m, 9H), 1.02–1.19 (m, 2H), 1.30–1.43 (m, 2H), 1.50–1.72 (m, 3H), 1.74 (s, 3H), 3.65 (brs, 3H, NH_3^+), 3.90 (t, J = 7.15 Hz, 1H), 3.99–4.05 (m, 1H), 7.19–7.23 (m, 1H), 7.26–7.34 (m, 4H), 7.68–7.70 (m, 2H) ppm. ^{13}C-NMR (50MHz, [D$_6$]DMSO) δ = 13.66 (q), 18.71 (t), 21.75 (q), 22.60 (q), 23.01 (q), 24.39 (d), 39.90 (t), 41.23 (t), 51.39 (d), 54.58 (d), 126.86 (d), 127.29 (d), 128.29 (d), 142.77 (s), 168.53 (s), 174.78 (s) ppm.



Less soluble salt of 3.65/5.4: ^{1}H-NMR (200MHz, [D$_6$]DMSO): δ = 0.64 (s, 3H), 0.75 (t, J = 7.21 Hz, 3H), 0.91 (s, 3H), 0.96–1.21 (m, 2H), 1.66–2.02 (m, 2H), 3.48 (dd, $^{3}J_{P\text{-}H}$ = 23.20, $^{2}J_{AB}$ = 10.75 Hz, 1H), 4.04 (dd, $^{3}J_{P\text{-}H}$ = 10.75, $^{2}J_{AB}$ = 2.20 Hz, 1H), 4.11 (t, 1H, J = 5.62 Hz, 1H), 5.53 (d, $^{3}J_{P\text{-}H}$ = 2.93 Hz, 1H), 7.27–7.51 (m, 9H), 8.68 (brs, NH_3^+, 3H). ^{13}C-NMR (50MHz, [D$_6$]DMSO) δ = 13.35 (q), 17.95 (q), 18.38 (t), 20.69 (q), 36.32 (t), 36.68 (s, $^{3}J_{C\text{-}P}$ = 2.29 Hz), 54.20 (d), 75.61 (t, $^{2}J_{C\text{-}P}$ = 4.96 Hz), 78.61 (d, $^{2}J_{C\text{-}P}$ = 4.58 Hz), 96.51 (d), 126.46 (d), 127.40 (d), 128.33 (d), 128.60 (d), 128.99 (d, $^{4}J_{C\text{-}P}$ = 11.44 Hz), 130.50 (d), 131.85 (s, $^{4}J_{C\text{-}P}$ = 1.00 Hz), 136.48 (s, $^{3}J_{C\text{-}P}$ = 9.54 Hz), 138.25 (s). ^{31}P-NMR (81MHz, [D$_6$]DMSO): δ = –5.26.



Conditions for HPLC Analysis

Entry	Substrate	HPLC column	Conditions	Ret. Times (min.)
1	 (±)-**5.2**	Chiralpak AD-H	heptane:*i*-propanol:TFA (95:5:0.1) 0.5 mL·min^{-1}	16.4 (*R*) 20.5 (*S*) (at λ = 220 nm)
2	 (±)-**5.3**	Chirobiotic T	methanol:acetic acid:TEA (99.5:0.1:0.1) 1.0 mL·min^{-1}	4.4 (*S*) 18.4 (*R*) (at λ = 210 nm)
3	 (±)-**5.4**	Chirobiotic R	methanol:acetic acid:TEA (99.5:0.4:0.1) 0.5 mL·min^{-1}	8.0 (*S*) 8.4 (*R*) (at λ = 225 nm)

5.6 References

[1] [1a] J. W. Nieuwenhuijzen, R. F. P. Grimbergen, C. Koopman, R. M. Kellogg, T. R. Vries, K. Pouwer, E. van Echten, B. Kaptein, L. A. Hulshof and Q. B. Broxterman, *Angew. Chem. Int. Ed.* **2002**, *41*, 4281–4286. [1b] J. W. Nieuwenhuijzen, *Resolutions with Families of Resolving Agents: Principles and Practice*; Ph. D. Thesis, University of Groningen, The Netherlands, **2002**. [1c] R. M. Kellogg, J. W. Nieuwenhuijzen, K. Pouwer, T. R. Vries, Q. B. Broxterman, R. F. P. Grimbergen, B. Kaptein, R. M. La Crois, E. de Wever, K. Zwaagstra and A. C. van der Laan, *Synthesis* **2003**, 1626–1638.

[2] A thorough and systematic description of performing resolution experiments is reported by Wilen *et al;* S. H. Wilen, A. Collet and J. Jacques, *Tetrahedron* **1977**, *33*, 2725–2736.

[3] D. Stickler, C. Clayton and J. Chawla, *Br. J. Urol.* **1987**, *60*, 413–418.

[4] http://www.cfb.de/pdf/Fine_Chemicals.pdf.

[5] http://www.sciens.com.cn/sciens/Product.htm.

[6] N. Bhana and K. J. McClellan *Drugs Aging.* **2001**, *5*, 369–388.

[7] The S-factor is a measure for the resolution efficiency and is described in section 1.6.2 of this thesis.

[8] The conditions and chiral HPLC-columns used for analysis are reported in the experimental section.

[9] Y. Yamamoto, H. Shimoda, J. Oda and Y. Inouye, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247–3249.

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Chapter 6
Nucleation Inhibition Studies in the Resolution of Chiral Acids

In this chapter, the second generation Dutch Resolution of racemic mandelic acid by (R)-1-phenylethylamine in the presence of potential family members is described in detail. 1-Phenylbutylamine proved to be a nucleation inhibitor and turbidity measurements were used to (a) quantify the kinetic effects involved, and (b) determine the minimal concentration of additive for which we still observe a nucleation inhibitory effect. A systematic study was performed to determine structure/activity relationships. About twenty potential family members of 1-phenylethylamine were screened as possible nucleation inhibitors. An important feature came to the fore; in most cases the racemic additives were almost as effective as the additives with the same configuration as the parent resolving agent and it was found that the "incorrect" enantiomer is also a modest nucleation inhibitor. On the basis of these and other experiments described, we are confident that for scouting purposes to find potential inhibitors, racemic (and sometimes more readily obtainable) additives may be used.

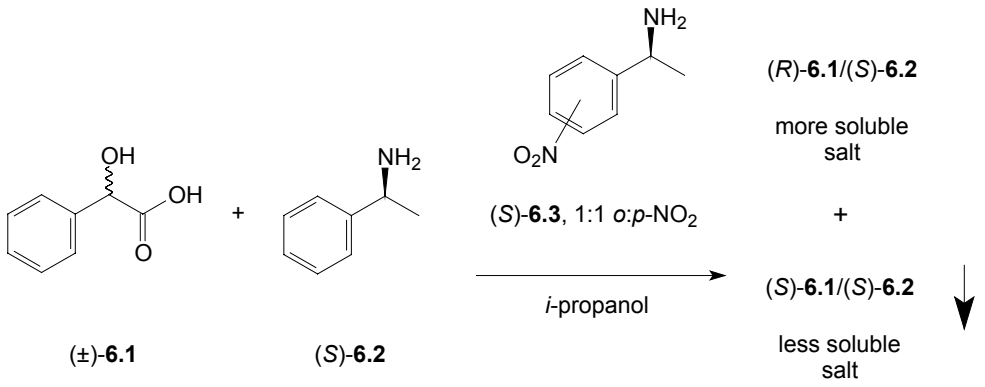
Part of this chapter is submitted for publication in *Angew. Chem. Int. Ed.*: J. Dalmolen, T. D. Tiemersma-Wegman, J. W. Nieuwenhuijzen, M. van der Sluis, B. Kaptein, R. M. Kellogg and Q. B. Broxterman.

6.1 Introduction

"Dutch Resolution" is the use of families of resolving agents in the otherwise classical Pasteur separation of racemates through their diastereomeric salts.[1] As first described an equimolar mixture of, in general, three resolving agents of the same family (close structural analogy, common absolute stereochemistry) was used. Non-stoichiometric incorporation of resolving agents and often improved diastereomeric excesses of the first salts are observed. In 10 of the 46 cases, no detectable amount of at least one of the resolving agents was found in the first isolated salts; in three other cases one of the resolving agents was present in < 10 mol % in the precipitated salts.

Further investigation revealed that certain family members of resolving agents, although they had a positive effect on the resolutions, in many cases were not, or only slightly, incorporated into the salts.[2] A model system was designed with two resolving agents. In this new approach (the *second* generation Dutch Resolution), the resolving agent present in the highest fraction is called the "parent resolving agent" and the component present in the smallest fraction is the "additive". The additive is typically a poorly or non-incorporated resolving agent.

An example is *ortho*/*para*-nitro mixture (*S*)-**6.3** used together with classical resolving agent 1-phenylethylamine (*S*)-**6.2** as illustrated for the case of the resolution of mandelic acid (Scheme 6.1). In this system, the more soluble diastereomeric salt is (*R*)-**6.1**/(*S*)-**6.2** and the less soluble diastereomeric combination is the (*S*)-**6.1**/(*S*)-**6.2** salt. All experiments were performed under non-optimal conditions, so that any improvement on addition of an additive could easily be detected.

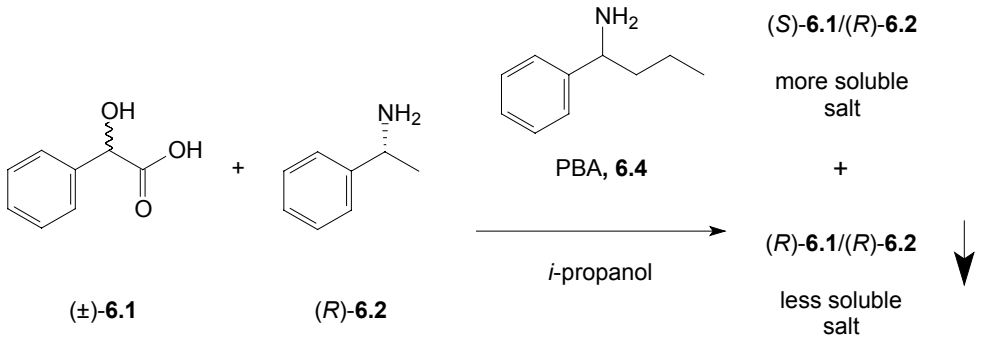


Scheme 6.1 *Second generation Dutch Resolution of* **(±)-*6.1*** *with (S)-**6.2** in the presence of 10 mol % **6.3** as an additive.*

In the absence of the additive, the resolution of (±)-**6.1** with (*S*)-**6.2** delivered a first salt with a diastereomeric excess (*de*) of 14 % and S-factor[3] of 0.19. When 10 mol % of (*S*)-**6.2** is substituted by a 1:1 mixture of *ortho*:*para* nitro-substituted (*S*)-1-phenylethylamine **6.3**, the *de* of the first isolated salt increased from 14 % to 55 % and the S-factor increased to 0.41. No detectable amount of either *ortho*- or *para*-(*S*)-**6.3** was found in the precipitated salt.[4] Turbidity measurements revealed that inhibitor **6.3** acts by widening the metastable zone width of supersaturation (the temperature zone between dissolution and the lower temperature at which precipitation begins) more for the better soluble diastereomer than for the less soluble diastereomer. In this chapter we search among other potential family members of parent resolving agent **6.2** for nucleation inhibitory effects.

6.2 1-Phenylbutylamine as an Additive

Additive (*S*)-**6.3**, a non-incorporated family member of (*S*)-**6.2**, has structural variation in the aryl ring. The availability of 1-phenylbutylamine (PBA, **6.4**)[5] led us to test the effect of structural variation in the side chain. In early experiments with 10 mol % of 1-phenylbutylamine as an additive, we observed a similar enhancement in the resolution process as in the experiments with 10 mol % of **6.3** (Scheme 6.2).

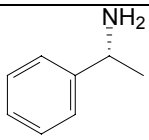
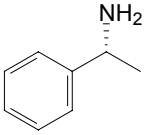
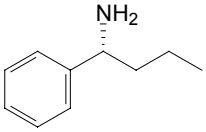
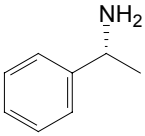
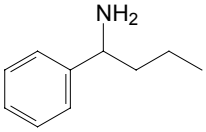
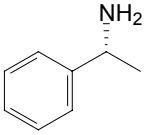
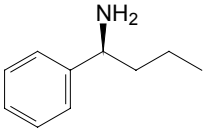
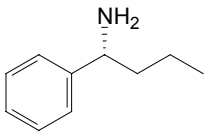


Scheme 6.2 *Second generation Dutch Resolution of (±)-**6.1** with (R)-**6.2** in the presence of 1-phenylbutylamine (PBA, **6.4**) as an additive.*

On substitution of 10 mol % of (*R*)-**6.2** with additive (*R*)-**6.4**, the *de* of the first salt increased from 14 % to 50 % (Table 6.2, entry 2), and an S-factor of 0.45 was obtained. Substitution of 10 mol % by racemic **6.4** gave a similar effect (entry 3). Remarkably, when 10 mol % of (*R*)-**6.2** was replaced by (*S*)-**6.4,** with the opposite configuration, a smaller but still significant improvement was observed (entry 4). In all cases, *no detectable amount of*

the additive was incorporated in the salts.[4] Enantiopure 1-phenylbutylamine itself is not a suitable resolving agent for **6.1,** under these conditions no salts precipitated (entry 5).

Table 6.1 *Dutch Resolution of (±)-**6.1** with (R)-**6.2**, in the absence and presence of 10 mol % **6.4** as an additive.*[6]

Entry	Resolving Agent	Additive	Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[c]
1	 (*R*)-**6.2**	–	–	68	14	0.19
2	 (*R*)-**6.2**	 (*R*)-**6.4**	10	45	50	0.45
3	 (*R*)-**6.2**	 (±)-**6.4**	10	44	49	0.43
4	 (*R*)-**6.2**	 (*S*)-**6.4**	10	63	25	0.31
5	 (*R*)-**6.4**	–		*No salts precipitate*		

Concentration = 0.40 mmol·mL^{-1} in *i*-propanol. [a] Isolated yield of the first salts. [b] *de* of the first isolated salts.[7] [c] S = 2 × yield × *de*.[3]

6.2.1 Turbidity Measurements

In resolution processes both kinetic and thermodynamic factors play a role. To quantify kinetic factors such as metastable zone width and nucleation inhibition, dynamic light scattering experiments were performed at the Center for Particle Technology at DSM Research in Geleen.

6.2.1.1 Experimental Set-up

A graphical representation of the experimental set-up of the turbidity measurements is given in Figure 6.1. All experiments were carried out in a 100 mL magnetically stirred flat-bottomed, jacketed glass vessel connected to a thermostatted bath that could be programmed. A laser beam (He/Ne, λ = 6328 Å) was directed through the vessel, and the onset of nucleation could be detected by measuring the "scattering" of the laser light through the solution. A computer was connected to monitor both the signal from the Pt100 digital thermometer in the solution, as well as the signal from the detector. In this manner, the scattering (which corresponds to the turbidity) and the temperature in the vessel could be measured as a function of time.[8] The sensitivity of the detector is adjusted in such a way that already at early stages of crystallization the maximum value for the turbidity of 5 (arbitrary units) is registered. A value close to 0 corresponds to a clear solution. With this technique, the temperature of dissolution and the temperature of crystallization could easily be detected, via the large change in turbidity.

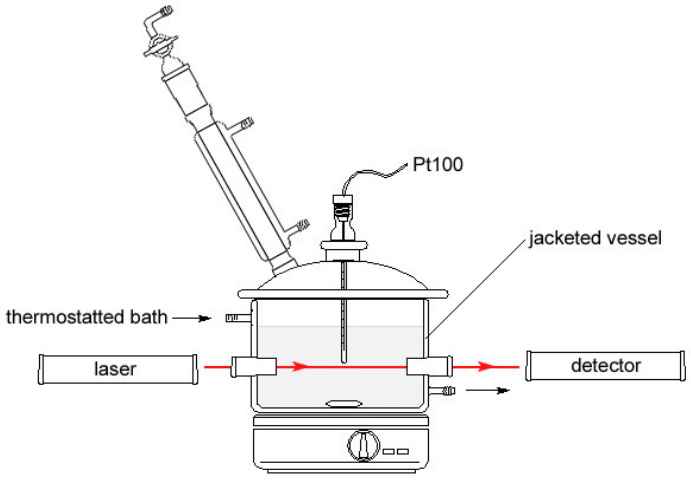


Figure 6.1 *Graphical representation of the experimental set-up used in turbidity measurements.*

6.2.1.2 Temperature Program

All experiments were subjected to the same temperature profile (Figure 6.2). In all cases, the ramp rate in the heating and cooling processes was the same as in the resolution experiments carried out in the Varian Thermostat, and was set to 10 °C per hour.

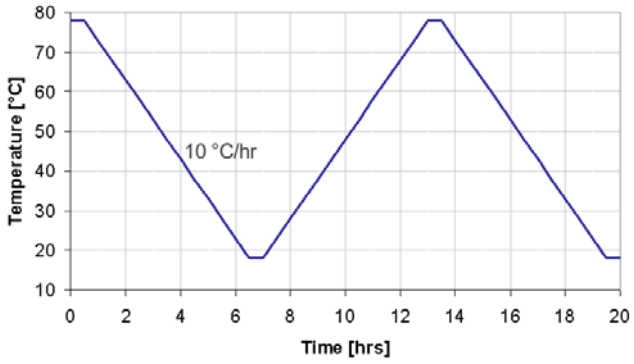


Figure 6.2 *Typical temperature profile used in the turbidity measurements.*

All experiments were started at 78 °C, and the content of the vessel was stirred at that temperature until a clear solution was obtained. Hereafter, the mixture was cooled to 18 °C, with a cooling rate of 10 °C per hour. After stirring for 0.5 hour at this temperature, the suspension was heated to 78 °C at the same rate, and stirred at that temperature for 0.5 hour to ensure dissolution of all nuclei. Subsequently, this cooling and heating cycle of 13 hours was repeated.

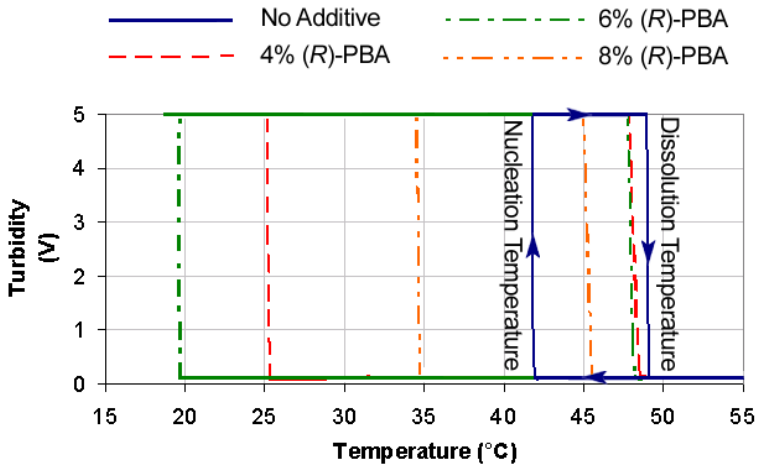
6.2.1.3 Determination of the Optimal Amount of Additive

From a cost-effective point of view it is more convenient to use 'catalytic' amounts of nucleation inhibitor as an additive (<10 mol %). This is why we performed turbidity measurements with various amounts of the additive to see at which concentration of additive we still observe a kinetic effect like delayed crystallization while thermodynamic effects (like solubility) remain unchanged.

Upon addition of a family member of the parent resolving agent, an inhibitory effect is observed for the nucleation of the more soluble diastereomeric combination as well as for the less soluble combination. In our experience, the effect is most pronounced in the more soluble diastereomeric combination at the concentrations used; therefore we performed the turbidity measurements with (*S*)-**6.1**/(*R*)-**6.2** and various amounts of additive (*R*)-**6.4** (Figure 6.3). At a certain concentration of the more soluble combination, (*S*)-**6.1**/(*R*)-**6.2** (without additive),[9] the dissolution temperature is 49.1 °C and the nucleation temperature is 41.8 °C (Figure 6.3 and Table 6.3). The area between the dissolution temperature and the nucleation temperature is called the 'metastable zone', and in this area the mixture is

supersaturated. The width of the metastable zone is indicative of the ease of formation of new nuclei, *i.e.* the broader the zone the slower nuclei form, and is determined by kinetic rather than thermodynamic factors.

Figure 6.3 and Table 6.2 *Nucleation and dissolution temperatures of the more soluble diastereomeric salt (S)-**6.1**/(R)-**6.2** at different concentrations of additive (R)-PBA (**6.4**).*



Entry	Amount of Additive	Nucleation Temp. (°C)	Dissolution Temp. (°C)	Width Metastable Zone (°C)
1	–	41.8	49.1	7.3
2	4 %	25.2	48.5	23.3
3	6 %	19.7	48.2	28.5
4	8 %	34.6	45.6	11.0

Once a critical level of supersaturation is reached, the system becomes labile and spontaneous crystallization will take place (primary nucleation).[10] Under the influence of 4 mol % and 6 mol % of (*R*)-**6.4**, the nucleation temperature changes significantly (entries 2 and 3), whereas the dissolution temperature stays more or less the same. The effect that the nucleation temperature is shifted to lower temperatures is called *nucleation inhibition*. As can be seen from the widths of the metastable zones, the nucleation inhibition effect is the largest at 6 mol % of additive. On substitution with ≥ 8 mol % of (*R*)-**6.4**, the dissolution temperature also changes substantially, which is probably due to an increase in solubility.

Since at 6 mol % of (*R*)-**6.4** the nucleation inhibition effect is most pronounced while thermodynamic factors remain unchanged, this concentration of additive was considered to be the optimal amount and was used for further measurements.

6.2.1.4 Measurements at the Optimal Amount of Additive

Because of the large difference in solubility, the more soluble diastereomeric salt (*S*)-**6.1**/(*R*)-**6.2** and the less soluble combination (*R*)-**6.1**/(*R*)-**6.2** were studied separately, and at different concentrations.[9,11]

6.2.1.4.1 The Effect of 6 Mol % of Additive on the More soluble Salt

In this section, the results of the turbidity measurements of the more soluble (*S*)-**6.1**/(*R*)-**6.2**, in the absence or presence of 6 mol % (*R*)-, (±)- and (*S*)-**6.4** will be discussed. As can be seen from Figure 6.4, on substitution of 6 mol % of (*R*)-**6.2** by either (*R*)-, (±)- or (*S*)-1-phenylbutylamine (PBA, **6.4**), the nucleation temperature shifted to lower temperatures to some extent. In all cases there is an substantial increase in metastable zone widths, whereas the dissolution temperatures remain the same (within the margin of error).[12] On substitution of 6 mol % (*R*)-**6.2** by (*S*)-**6.4**, the nucleation temperature shifts from 41.8 °C to 34.8 °C (Table 6.3, entry 4), and the metastable zone width is increased from 7.3 °C to 13.0 °C, an enlargement of 178 %. In the case of 6 mol % of (*R*)- or (±)-**6.4** as an additive (entries 2 and 3), the metastable zone width increases even more drastically, 28.2 °C and 25.3 °C respectively (an enlargement of 390 % and 347 %, respectively).

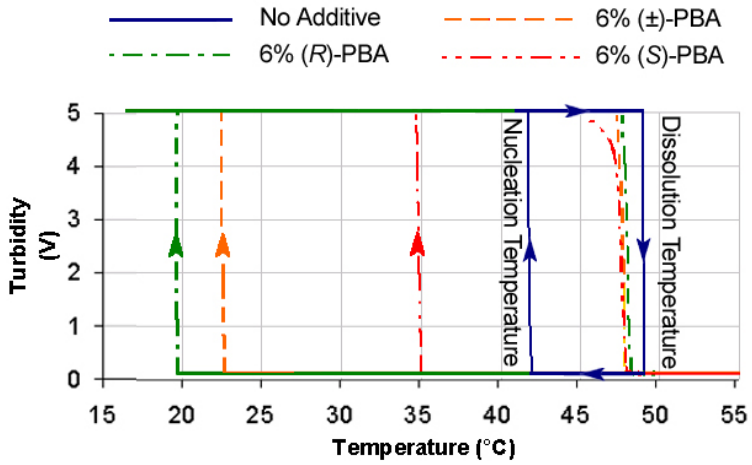


Figure 6.4 *Turbidity measurements on the more soluble diastereomeric salt (S)-**6.1**/(R)-**6.2** in the absence and presence of 6 mol % of (R)-, (±)- or (S)- **6.4**.*

Table 6.3 *Nucleation and dissolution temperatures of the more soluble (S)-**6.1**/(R)-**6.2** in the absence and presence and 6 mol % of (R)-, (±)- or (S)- **6.4**.*

Entry	Additive	Nucleation Temp. (°C)	Dissolution Temp. (°C)	Metastable Zone Width (°C)
1	–	41.8	49.1	7.3
2	6% (*R*)-**6.4**	19.7	48.2	28.5
3	6 % (±)-**6.4**	22.5	47.8	25.3
4	6% (*S*)-**6.4**	34.8	47.8	13.0

6.2.1.4.2 The Effect of 6 Mol % of Additive on the Less Soluble Salt

In all cases, replacement of 6 mol % of (*R*)-**6.2** by 1-phenylbutylamine (PBA, **6.4**) led to a shift in nucleation temperatures (Figure 6.5).

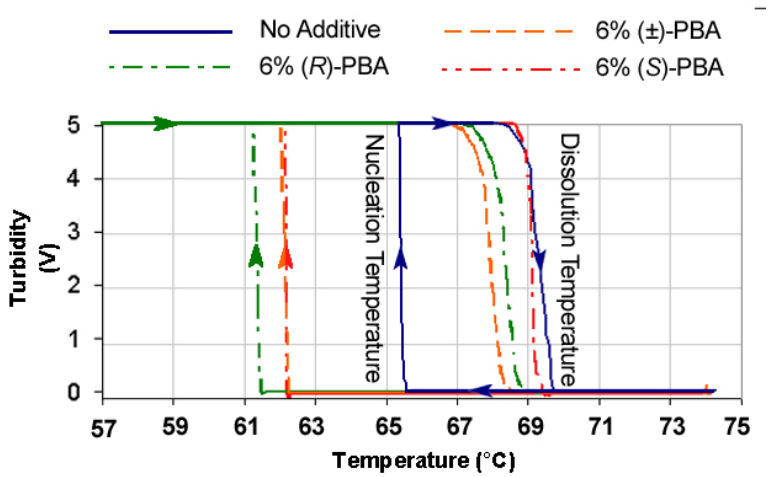


Figure 6.5 *Turbidity measurements on the less soluble diastereomeric salt (R)-**6.1**/(R)-**6.2** in the absence and presence of 6 mol % of (R)-, (±)- or (S)-**6.4**. Since the inhibitory effect is less pronounced compared to the more soluble, the temperature scale differs from Figure 6.3 and 6.4.*

From the nucleation- and dissolution temperatures listed in Table 6.4, it can be seen that the metastable zones are only slightly enlarged, and that the effect of the additive is less strongly pronounced on the less soluble salt. In all cases the dissolution temperatures remain more or less the same (within the margin of error).[12]

Table 6.4. *Nucleation and dissolution temperatures of the less soluble (R)-**6.1**/(R)-**6.2** in the absence and presence of 6 mol % of (R)-, (±)- or (S)-**6.4**.*

Entry	Additive	Nucleation Temp. (°C)	Dissolution Temp. (°C)	Metastable Zone Width (°C)
1	–	65.4	69.3	3.9
2	6% (*R*)-**6.4**	61.4	68.4	7.0
3	6 % (±)-**6.4**	62.1	68.0	5.9
4	6% (*S*)-**6.4**	62.1	69.2	7.1

6.2.2 Resolution Experiments with 6 Mol % of 1-Phenylbutylamine

Since at 6 mol % of **6.4** the nucleation inhibition effect is the most pronounced, and the solubility is unaffected, we decided to repeat the second generation Dutch Resolution experiments with this amount of additive. The results are presented in Table 6.5.

Table 6.5 *Second generation Dutch Resolution of (±)-**6.1** with (R)-**6.2**, in the absence and presence of 6 mol % **6.4** as an additive.*[6]

Entry	Resolving Agent	Additive	Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[c]
1	(*R*)-**6.2**	–	–	68	14	0.19
2	(*R*)-**6.2**	(*R*)-**6.4**	6	60	42	0.50
3	(*R*)-**6.2**	(±)-**6.4**	6	62	35	0.43
4	(*R*)-**6.2**	(S)-**6.4**	6	61	30	0.37

Concentration = 0.40 mmol·mL^{-1} in *i*-propanol. [a] Isolated yield of the first salts. [b] *de* of the first isolated salts.[7] [d] S = 2 × yield × *de*.

These results are in agreement with the observations from the turbidity measurements: the largest effect was observed on substitution of 6 mol % by (*R*)-**6.4;** a first isolated salt was obtained with a *de* of 42 % and an S-factor of 0.50 (entry 1). As in the turbidity measurements, the effect of nucleation inhibition was somewhat smaller on substitution by

6 mol % of racemic **6.4**; this resolution delivered a first salt with a *de* of 35 % and an S-factor of 0.43. The degree of recognition of the nucleation inhibitor is modestly enantioselective; substitution by 6 mol % of the additive with the opposite configuration gave a smaller, but still significant, effect on the resolution. Performance of the reaction of entry 2 on a 10 gram (65.8 mmol) scale led within 1 % to the same yield, *de* and S-factor as the 2 mmol scale used in Table 6.5.

6.2.3 Temperature Effect on the Resolution

The solubility of the diastereomeric salts is strongly dependent on the temperature; therefore the resolution efficiency is also temperature dependent. By isolating and analyzing the crystallized material during the cooling process, the crystallization behaviour as a function of temperature can be determined.

The effects of additive (*R*)-**6.4** on the yield, *de* of the first salt and the accompanying S-factor in the resolution of **6.1** with (*R*)-**6.2** between is depicted in Figure 6.6a–c. The monitored temperature range is from 70 °C and 0 °C. On cooling, the amount of crystallized material starts to increase in an almost linear fashion; but around ambient temperatures the yield starts to stabilize in the presence of (*R*)-**6.4**.

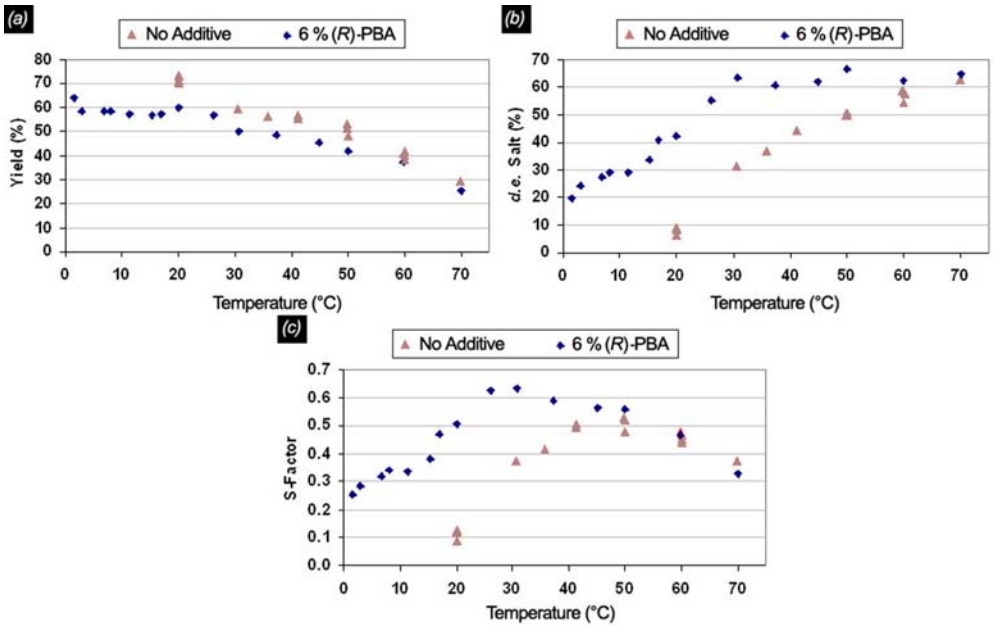


Figure 6.6a–c *Crystallization behaviour as a function of temperature in the absence and presence of (R)-**6.4**.*

At any given temperature the yield is only slightly lower in the presence of (*R*)-**6.4** than in the absence of additive (Figure 6.6a). We believe that the nucleation inhibition effect can also be observed in Figure 6.6b. Without additive the *de* of the first salt decreases rapidly on cooling, but in the presence of (*R*)-**6.4** the *de* of crystallized material remains high and unchanged until ± 30 °C. This results in a higher maximum resolution efficiency, which is typically shifted to lower temperatures when a nucleation inhibitor is used (Figure 6.6c). Herein lies the success of Dutch Resolution; with correct temperature control, more opportunity for selective precipitation of the less soluble diastereomeric salt is achieved. The same conclusion can be derived by constructing ternary phase diagrams, as already described by Nieuwenhuijzen *et al*.[2a,b] In principle, it would be advizable to screen a resolution process at different temperatures.

6.3 Screening for Other Possible Nucleation Inhibitors

Because of the significant improvements in resolvability on addition of **6.4** as a nucleation inhibitor, a systematic study was carried out. We screened about twenty potential family members of 1-phenylethylamine as possible nucleation inhibitors (Figure 6.7).

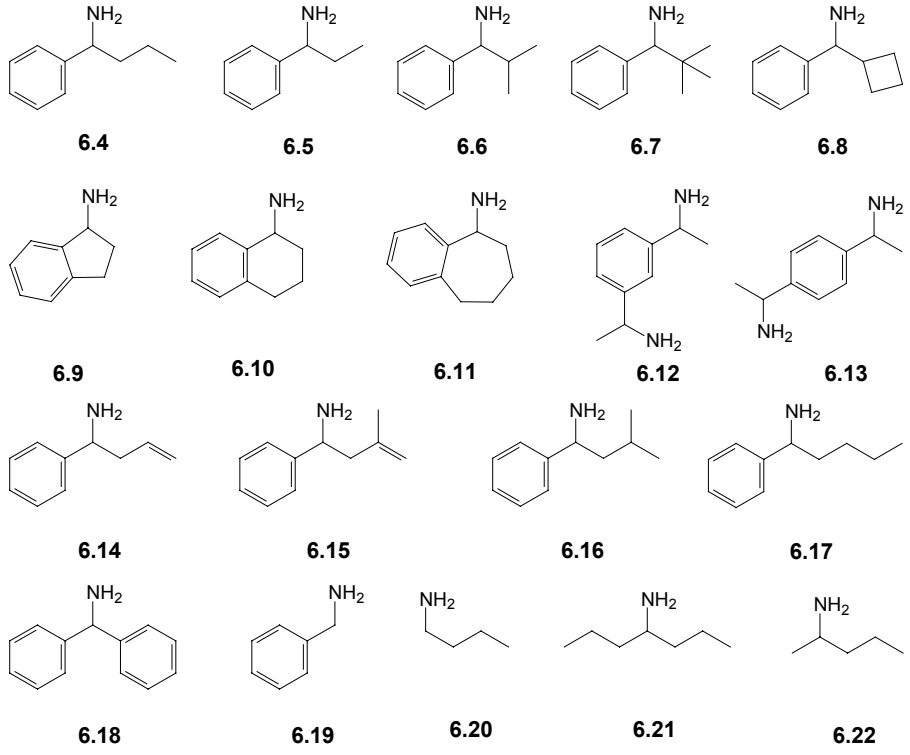
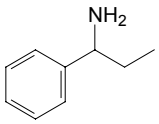
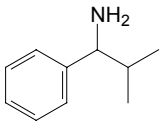
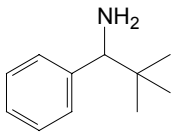
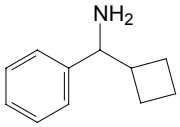
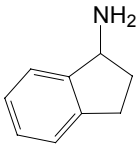
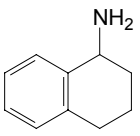
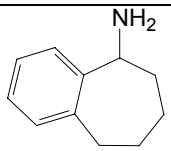
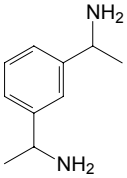
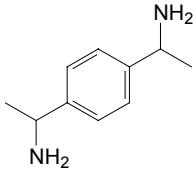
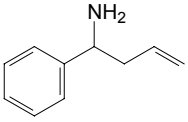
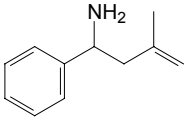
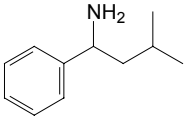
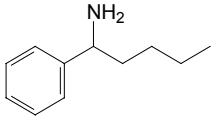
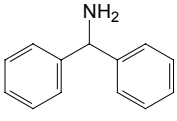


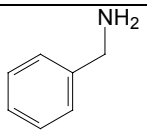
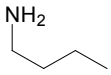
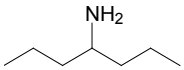
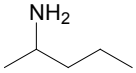
Figure 6.7 *Possible nucleation inhibitors tested in Dutch Resolution experiments.*[13]

To clarify the role of the structural aspects, additives with branched tails or different tail lengths (**6.5**–**6.8** and **6.14**–**6.17**),[13] additives with cyclic tails (**6.9**–**6.11**), achiral additives **6.18**–**6.21**, additives that lack the phenyl ring (**6.20**–**6.22**) and the *meta*- and *para*-diamino additives (**6.12** and **6.13**) were tested. It does not seem reasonable that every small change in the structure of a resolving agent will automatically lead to a nucleation inhibitor. The results of the experiments under Dutch Resolution conditions with these potential nucleation inhibitors as an additive are summarized in Table 6.6 and Figure 6.8.

Table 6.6 *Screening for potential nucleation inhibitors in the second generation Dutch Resolution of (±)-**6.1**.*[6]

Entry	Additive	Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[d]
1	No additive	–	68	14	0.19
2	 (±)-**6.5**	6	66	30	0.40
3	 (±)-**6.6**	6	57	40	0.46
4	 (±)-**6.7**	6	63	17	0.21
5	 (±)-**6.8**	6	64	19	0.24
6[a]	 (*R*)-**6.9**		59	34	0.40
6[b]	(±)-**6.9**	6	63	29	0.37
6[c]	(*S*)-**6.9**		67	20	0.27
7[a]	 (*R*)-**6.10**		66	25	0.33
7[b]	(±)-**6.10**	6	66	22	0.29
7[c]	(*S*)-**6.10**		67	17	0.23

Entry	Additive		Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[d]
8		(±)-**6.11**	6	60	24	0.29
9		(±)-**6.12**	3 6	50 51	58 42	0.58 0.43
10		(±)-**6.13**	3 6	64 50	44 45	0.56 0.45
11[a]		(*R*)-**6.14**		62	34	0.42
11[b]		(±)-**6.14**	6	64	32	0.41
11[c]		(*S*)-**6.14**		62	31	0.38
12[a]		(*R*)-**6.15**		57	26	0.29
12[b]		(±)-**6.15**	6	57	23	0.26
12[c]		(*S*)-**6.15**		61	16	0.20
13		(*R*)-**6.16**	6	59	39	0.46
14		(±)-**6.17**	6	62	22	0.27
15		**6.18**	6	62	22	0.28

Entry	Additive		Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[d]
16		**6.19**	6	67	18	0.24
17		**6.20**	6	65	23	0.30
18		**6.21**	6	62	16	0.20
19		(±)-**6.22**	6	65	29	0.38

Concentration = 0.40 mmol·mL^{-1} in *i*-propanol. [a] Isolated yield of the first salts. [b] *de* of the first isolated salts.[7] [d] S = 2 × yield × *de*.

As a blank reaction, a resolution experiment was performed in which 6 mol % of the parent resolving agent (*R*)-**6.2** was replaced by 6 mol % of the solvent. In general, on going to lower concentrations of salt, the yield decreases and the *de* of the salt increases. When 0.94 mol equivalents of the parent resolving agent (*R*)-**6.2** was used, a first salt was obtained with an isolated yield of 73 % and a *de* value of 17 %, which leads to a comparable S-factor of 0.24 (Figure 6.8). As a "hit" is arbitrarily defined as S ≥ 0.35 relative to this S = 0.24.

In 9 out of the 18 systems tested, there were no significant improvements in the *de* values of the first obtained salts. As can be seen from the S-factors (Table 6.6 and Figure 6.8), achiral additives **6.18**–**6.21** (entries 14–17) did not lead to meaningful improvement of the resolvability. In all cases, no detectable amounts of the additives were found in the isolated salts.[4]

There is a delicate balance between branching on the alkyl chain and additives with different tail lengths. For instance, when additive **6.5** is compared with additive **6.6**, branching on the α-position enhances the resolvability. Although the yields more or less remains similar, the *de* values of the first salt increase from 30 % to 40 % (and hence the S-factor increases). Further branching on the α-position (additive **6.7**), decreases the efficiency of the resolution dramatically and the effect of nucleation inhibition is diminished. The same effect can be seen when additive **6.4** is compared to additive **6.16**; branching on the β-position of the alkyl chain leads to deterioration of the S-factors. When unsaturated additives **6.14** and **6.15** are compared, branching on the β-position has no significant effect, and no further enhancement of the resolvability is observed.

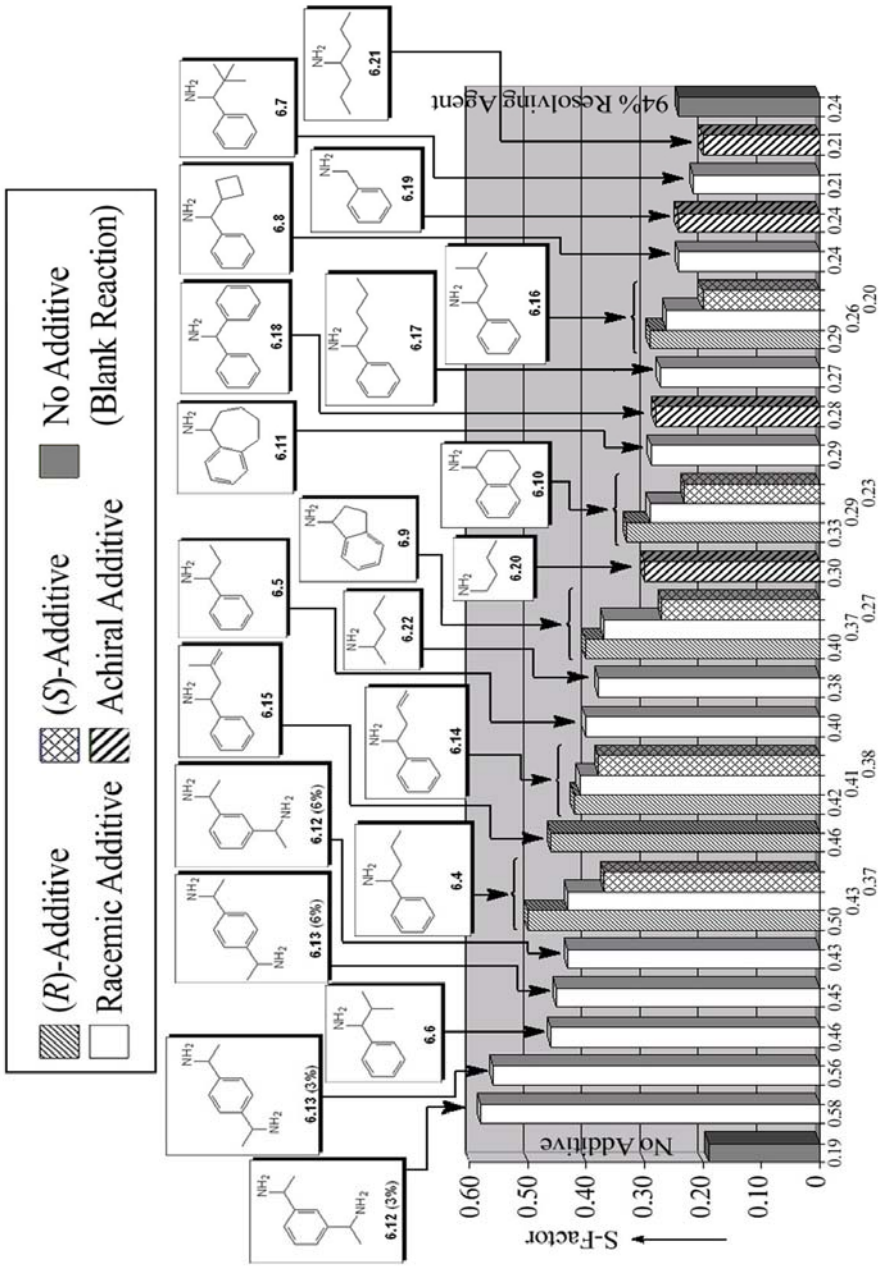


Figure 6.8. *S-Factors in the screening of new possible nucleation inhibitors.*

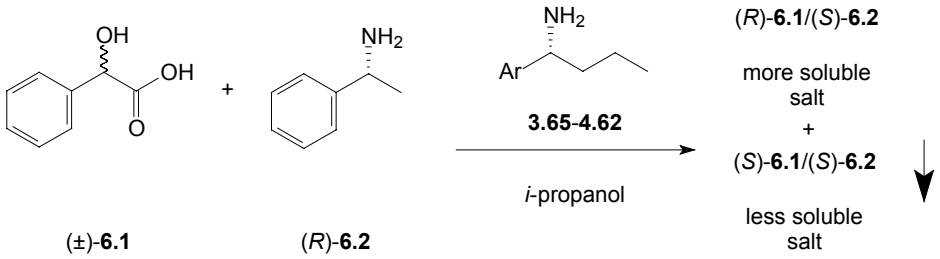
Going from 1-phenylpropylamine **6.5** to 1-phenylbutylamine **6.4**, there is a clear positive effect noticable on elongation of the tail by one carbon atom. On further elongation of the alkyl side chain of the additive, no significant effect is observed at all, as can been seen from resolutions in the presence of 6 mol % **6.17**. The effect on the resolvability using the *ortho*- and *para*-substituted diamino additives **6.12** and **6.13** is noteworthy; on addition of 3 mol % of either racemic **6.12** or **6.13**, the S-factors increase to 0.58 and 0.56, respectively. In both cases, the use of 6 mol % of **6.12** or **6.13** showed smaller improvements.

In general, the S-factors depicted in Figure 6.8 indicate that the racemic additives only show a slightly poorer effect compared to the additives with the same configuration as the parent resolving agent. This makes the screening process considerably easier; in the search for suitable nucleation inhibitors racemic family members can be used. Once a suitable nucleation inhibitor is found in this screen, the enantiopure additive might probably enhance the resolvability even further. When additives are used with the opposite configuration of the parent resolving agent, the effect of nucleation inhibition is clearly less pronounced but yet significant. This observation again emphasizes the enantioselective recognition in the resolution process, and consolidates the "family behaviour".

In the presence of an additive, the crystallized material had a less well-defined crystal habit and the crystals were considerably smaller. If this is due to adsorption of the additive on specific faces (and acting as a habit modifier),[14] due to delayed crystallization, or a combination of both is not clear. Since the amount of solute that can crystallize from solution is fixed, a larger number of nuclei formed per time unit (because supersaturation increases) must result in each crystal being smaller.

6.4 1-Arylbutylamines as Possible Nucleation Inhibitors

Because of the satisfactory results obtained with 6 mol % of 1-phenylbutylamine as an additive, we wondered whether substitution on the aromatic ring or modification of the ring structure itself might further enhance the resolution efficiency. Second generation Dutch Resolution experiments were performed with 6 mol % of the 1-arylbutylamines **3.65**–**4.62** as an additive (Scheme 6.3). The syntheses of these arylbutylamines are described in Chapter 3 and 4 of this thesis.



Scheme 6.3 *Screening for potential nucleation inhibitors in the second generation Dutch Resolution of (±)-**6.1** in the presence of 6 mol % of 1-arylbutylamines as an additive.*

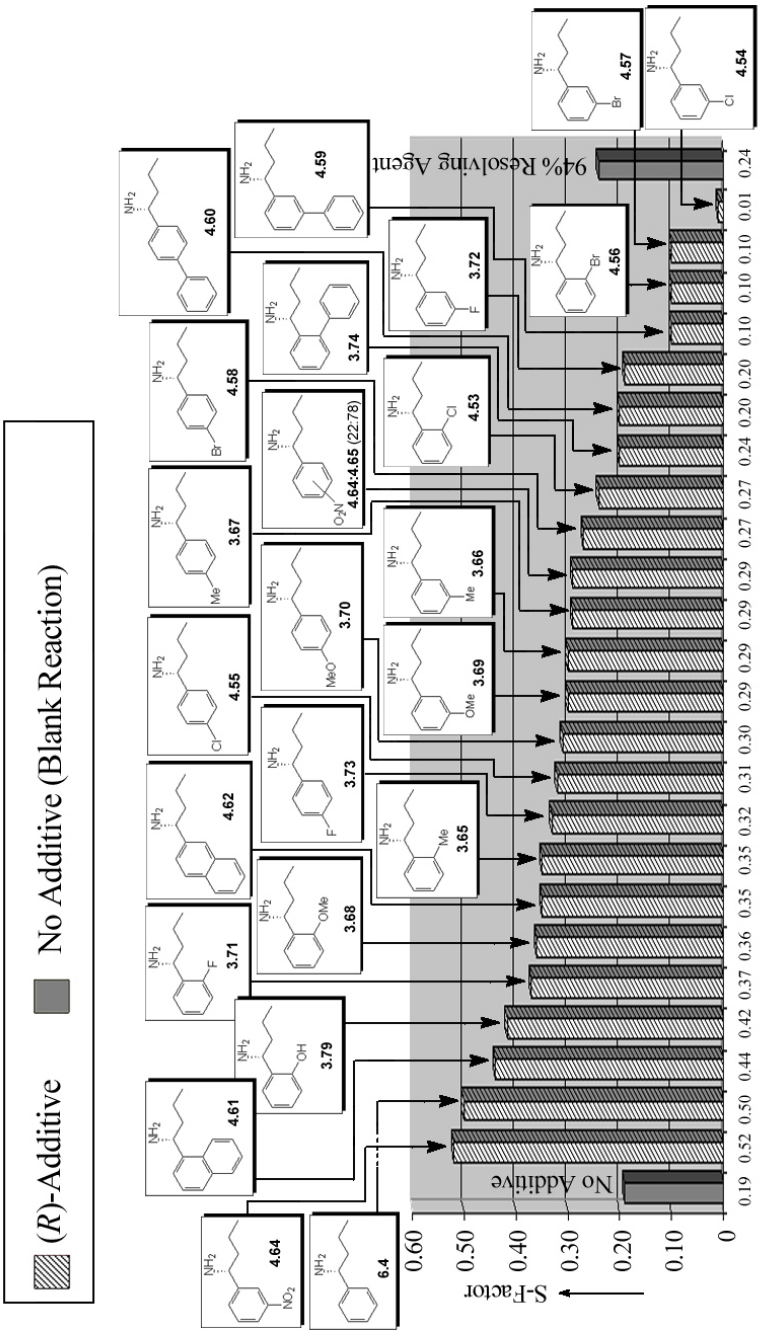


Figure 6.9 *S-Factors in the screening of the family of 1-arylbutylamines.*

In virtually all cases, the yields in the second generation Dutch Resolution experiments do not differ that much from that of the control experiment without additive (Table 6.7). This means that any variation in S-factors is due to changes in the *de* value of the first isolated salts. Most substituents do not further improve the resolvability, and in some cases a drop in *de* is observed. For instance, when 6 mol % of additive **4.54** was used, a first salt was obtained without diastereoselectivity (Table 6.7, entry 13). The S-factors presented in Figure 6.9 make clear that little tolerance is allowed in the substitution on the aromatic ring.

Table 6.7 *Screening for potential nucleation inhibitors in the second generation Dutch Resolution of (±)-**6.1** in the presence of 6 mol % of 1-arylbutylamines as an additive.*[6]

Entry	Additive		Yield	*de*	S
	Ar	1-Arylbutylamine	(%)[a]	(%)[b]	Factor[d]
1	No additive	–	68	14	0.19
2	C_6H_5	**6.4**	60	42	0.50
3	*o*-Me C_6H_4	**3.65**	64	27	0.35
4	*m*-Me C_6H_4	**3.66**	63	24	0.30
5	*p*-Me C_6H_4	**3.67**	66	22	0.29
6	*o*-OMe C_6H_4	**3.68**	62	29	0.36
7	*m*-OMe C_6H_4	**3.69**	59	25	0.30
8	*p*-OMe C_6H_4	**3.70**	74	21	0.31
9	*o*-F C_6H_4	**3.71**	62	30	0.37
10	*m*-F C_6H_4	**3.72**	63	23	0.29
11	*p*-F C_6H_4	**3.73**	65	25	0.33
12	*o*-Cl C_6H_4	**4.53**	67	18	0.24
13	*m*-Cl C_6H_4	**4.54**	66	1	0.01
14	*p*-Cl C_6H_4	**4.55**	60	27	0.32
15	*o*-Br C_6H_4	**4.56**	65	8	0.10

Entry	Additive		Yield (%)[a]	*de* (%)[b]	S Factor[d]
	Ar	1-Arylbutylamine			
16	*m*-Br C_6H_4	**4.57**	64	8	0.10
17	*p*-Br C_6H_4	**4.58**	62	20	0.27
18	*o*-Ph C_6H_4	**3.74**	64	16	0.20
19	*m*-Ph C_6H_4	**4.59**	57	9	0.10
20	*p*-Ph C_6H_4	**4.60**	67	15	0.20
21	*o:p*-NO_2 C_6H_4	**4.63:4.64** (22:78)	63	23	0.29
22	*m*-NO_2 C_6H_4	**4.68**	59	44	0.52
23	*o*-OH C_6H_4	**3.79**	67	31	0.42
24	1-naphthyl	**4.61**	58	38	0.44
25	2-naphthyl	**4.62**	64	27	0.35

Concentration = 0.40 mmol·mL^{-1} in *i*-propanol. [a] Isolated yield of the first salts. [b] *de* of the first isolated salts.[7] [d] S = 2 × yield × *de*.

6.5 Direct HPLC-Analysis of the First Salts

Generally, for HPLC-analysis, the substrate to be investigated has to be liberated from the salt; this liberation step involves: (a) adjusting the pH, (b) extraction with an appropriate solvent, (c) drying the solvent/substrate-mixture over sodium sulphate, (d) removal of the solvent *in vacuo* and subsequently (d) prepare the sample for HPLC-analysis (in the appropriate eluent). In particular this time-consuming liberation step hampers a quick analysis, which is necessary in every screening process. Therefore, we developed a direct analysis method of the first isolated salts by tuning the conditions of the HPLC-analysis. This 'direct salt analysis'[15] must meet the following requirement: in the HPLC chromatogram neither the parent resolving agent nor the additive must interfere with the retention-times of the substrate of interest. An example can be seen in Figure 6.10; in this example 1-phenylbutylamine was *added* to the HPLC-sample to show that all possible components (additive, parent resolving agent, and both enantiomers of the substrate) have well defined and well separated retention times. This requirement was thoroughly tested for all additives independently; all additives had retention-times typically between 5 and 17 minutes.

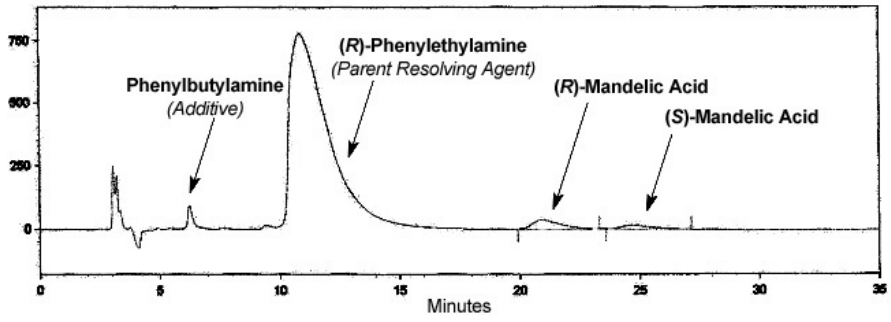
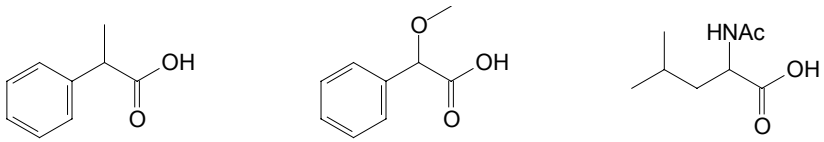


Figure 6.10 *HPLC chromatogram of the "direct-salt-analysis".*

In some cases (like in the example depicted in Figure 6.10), it also appeared to be possible to determine the diastereomeric excess and the amount of additive in the first isolated salts (*if present!)* in one run. In all reported cases of the top-5 additives, there were no detectable amounts (HPLC, NMR, mass analysis) of additives present in the salt.

6.6 Other Systems Put to the Test

To extend the results obtained with mandelic acid as a racemate, other systems were subjected to the second generation Dutch Resolution experiments as described in section 6.3 in this chapter. Hydratropic acid (**6.23**), α-methoxyphenylacetic acid (**6.24**) and *N*-acetyl-DL-leucine (**6.25**) were tested with the "top 5" (racemic) additives from Figure 6.8 that gave a S > 0.35. [†]



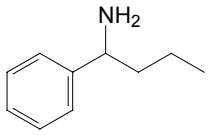
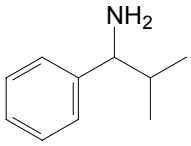
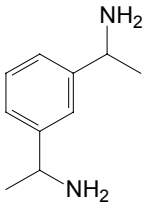
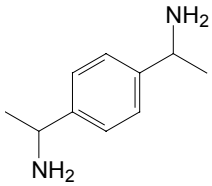
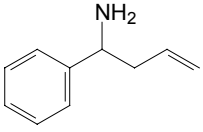
6.23 **6.24** **6.25**

6.6.1 Hydratropic Acid

The (*S*)- and (*R*)-isomers of hydratropic acid (2-phenylpropionic acid, **6.23**) are chiral derivatizing agents that have been used for the assignment of the absolute configuration of alcohols,[16] amines[17] and thiols[18] by ^{1}H-NMR.

[†] *The direct HPLC-analysis of the first salts was also convenient for substrates **6.23** and **6.24**.*[15]

Table 6.8 *Second generation Dutch Resolution of hydratropic acid* ***6.23*** *with (R)-****6.2*** *in the absence and presence of 3 or 6 mol % of an additive.*[6]

Entry	Additive	Additive (%)	Yield (%)	*de* (%)	S Factor
1	–	–	60	7	0.08
2	 (±)-**6.4**	6	54	39[a]	0.43
3	 (±)-**6.6**	6	48	20[a]	0.19
4[a]	 (±)-**6.12**	3	36	59[a]	0.43
4[b]		6	49	36[a]	0.35
5[a]	 (±)-**6.13**	3	54	52[a]	0.56
5[b]		6	43	63[a]	0.55
6	 (±)-**6.14**	6	50	49[a]	0.49

Concentration = 0.30 mmol·mL^{-1} in *i*-propanol:H_2O (20:1). [a] Crystallized material contained the (*R*)-**6.2**/(*S*)-**6.23** in excess.

Standard resolution experiments of racemic **6.23** with (*R*)-1-phenylethylamine **6.2** without additives gave very poor results; a first salt was isolated with a *de* value of 7 % and a corresponding S-factor of 0.08 (Table 6.8). In general, all additives that were screened showed typical nucleation inhibitory effects and improvement of the resolution process, Crystallized material contained the (*R*)-**6.2**/(*S*)-**6.23** in excess. A few cases will be highlighted.

Best results were obtained with 1,4-diamino additive **6.13**. Whereas on addition of only 3 mol % **6.13** (entry 5^a) the yield of the first salt only decreases slightly compared to the blank reaction, the *de* of the first salt was increased from 7 % to an impressive 52 %. On addition of slightly more **6.13** (6 mol %, entry 5^b) the nucleation inhibition effect becomes even more pronounced. The *de* is increased to 63 % but since the yield slightly drops, entries 5^a and 5^b give comparable resolution efficiencies.

The 1,3-diamino additive **6.12** showed slightly lower but still satisfactory S-factors (entries 4^a and 4^b). The highest *de* of the first salt was obtained with 3 mol % of **6.12** (S-factor of 0.43). The fact that on addition of more **6.12** (entry 4^b) the resolution efficiency decreases again in this case, emphasizes the fact that there is an optimum amount of additive that has to be used. Once a hit is found, one should also "fine-tune" the mol percentage of additive.

Both 6 mol % of unsaturated additive **6.14** and its saturated counterpart **6.4** still showed satisfactory S-factors of S > 0.35.

6.6.2 α-Methoxyphenylacetic Acid

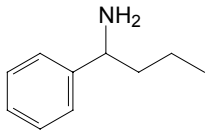
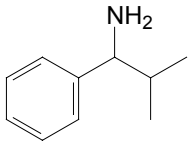
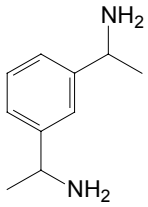
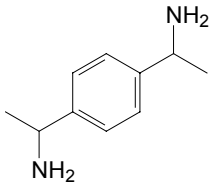
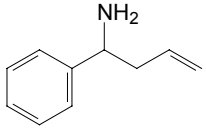
α-Methoxyphenylacetic acid (**6.24)** was used in the synthesis of chiral phosphine ligands[19] and, like hydratropic acid, both enantiomers of **6.24** are reagents for assignment of absolute stereochemistry by NMR.[20] Recently, a number of α-methoxyphenylacetic acid derivatives showed potent fungicidal activity against a wide range of crop diseases.[21]

In the resolution of racemic **6.24** with (*R*)-**6.2** in the absence of additive, a salt precipitated with essentially no diastereoselectivity (Table 6.9, entry 1).

After gradual cooling in the thermostatted bath and a waiting period of 12 hours, no salts precipitated in the cases where 1,3-diamino compound **6.12** was used. The clear solutions were left untouched and stirred at ambient temperatures until some material precipitated. While in the case of 3 mol % **6.12** after three additional days a salt precipitated with a *de* of 36 % and an S-factor of 0.39, in all three tubes where 6 mol % of **6.12** was used persistently no material crystallized. After an additional three days, in one of the three tubes a salt precipitated in a yield of 16 % with an astonishing *de* of 96 %. Unfortunately, the other two tubes remained clear.

As in the case of resolution of hydratropic acid and mandelic acid, family members **6.4** and **6.14** showed similar typical nucleation inhibitory effects; both led to a slight decrease in yield while the *de* increased significantly.

Table 6.9 *Second generation Dutch Resolution α-methoxyphenylacetic acid* ***6.24*** *with (R)-* ***6.2*** *in the absence and presence of 3 or 6 mol % of an additive.*[6]

Entry	Additive	Additive (%)	Yield (%)	*de* (%)	S Factor
1	–	–	65	1	0.02
2	 (±)-**6.4**	6	40	40[a]	0.32
3	 (±)-**6.6**	6	49	17[a]	0.16
4[a]	 (±)-**6.12**	3	54 [b]	36[a]	*0.39*
4[b]		6	16 [c]	96[a]	*0.30*
5[a]	 (±)-**6.13**	3	31	40[a]	0.19
5[b]		6	29	20[a]	0.11
6	 (±)-**6.14**	6	42	32[a]	0.27

Conc. = 0.25 mmol·mL^{-1} in *i*-propanol:H_2O (20:1). [a] Crystallized material contained the (*R*)-**6.2**/(*R*)-**6.24** in excess. [b] Salts isolated after 3 days. [c] Isolated after 6 days.

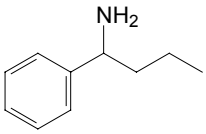
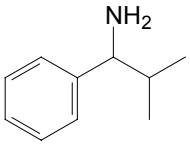
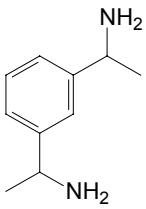
6.6.3 *N*-Acetylleucine

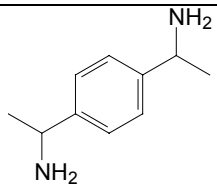
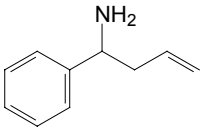
In the standard resolution of *N*-acetyl-DL-leucine **6.25**, a resolving agent itself, with (*R*)-PEA **6.2** and in absence of additive, a salt precipitated in 58 % yield with a low *de* value of 13 % (Table 6.10, entry 1).

Like in all previous substrates tested, addition of either 6 mol % of (±)-**6.4** or (±)-**6.14** showed similar improvements in resolution efficiencies. In this case, although the slight decrease in yield, resolution efficiencies are increased to S ≥ 0.39 (entries 2 and 8). Addition of additives **6.6** and **6.12** showed only minor improvements (entries 3 and 4).

Best results were obtained with *para*-diamino additive **6.13**. On addition of both 3 mol % and 6 mol % of racemic **6.13**, the *de* is increased to a phenomenal 75 % (entries 5[a] and 5[b]). Since both concentrations of additive give the same result, it could well be that there is a maximum in S-factor between 3 and 6 mol % (not determined).

Table 6.10 *Second generation Dutch Resolution of N-acetylleucine* ***6.25*** *with (R)-****6.2*** *in the absence and presence of 3 or 6 mol % of an additive.*

Entry	Additive	Additive (%)	Yield (%)	*de* (%)[a]	S Factor
1	–	–	58	13	0.15
2	 (±)-**6.4**	6	49	40	0.39
3	 (±)-**6.6**	6	52	31	0.32
4[a]	 (±)-**6.12**	3	44	31	0.27
4[b]		6	45	36	0.32

Entry	Additive	Additive (%)	Yield (%)	*de* (%)[a]	S Factor
5[a]	 (±)-**6.13**	3	35	75	0.53
5[b]		6	33	75	0.50
6	 (±)-**6.14**	6	47	45	0.42

Concentration = 0.75 mmol·mL^{-1} in *i*-propanol:H_2O (5:2). [a] Crystallized material contained the (*R*)-**6.2**/(*R*)-D-**6.25** in excess.

6.7 Possible Role of the Nucleation Inhibitor

A model to explain how adsorbed particles can affect crystal growth was already presented in Chapter 2 (Figure 6.11*a*). To our opinion this model can also be used to a certain extent for nucleation inhibition. However, since this model also holds for 'ordinary' impurities, the question remains when an impurity becomes a family member of the parent resolving agent and therefore a potential nucleation inhibitor.

The (inhibited) nucleation of mandelic acid with 1-phenylethylamine in a resolution process is depicted in cartoon form in Figure 6.11*b*. The crystal forming elements are represented as pieces of a jigsaw puzzle; the 'connecting parts' of the puzzle pieces symbolize possible interactions (*e.g.* electrostatic interactions). Each layer consists of two crystal-forming elements; a 'mandelic acid puzzle piece' and a '1-phenylethylamine puzzle piece'. In a (Dutch) resolution experiment, there are two of these jigsaw puzzles to be resolved; one puzzle for the more soluble combination and one for the less soluble combination.

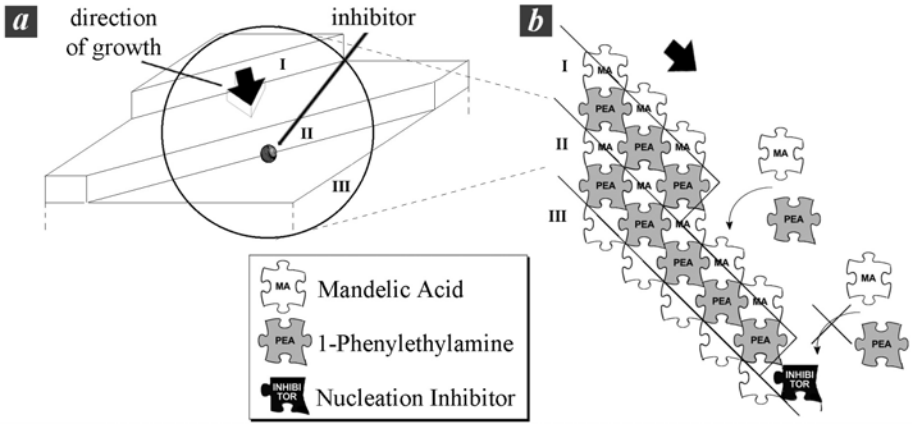


Figure 6.11. *(a) Growth inhibition at an active growth site blocked by an inhibitor; (b) nucleation inhibition at the early stage of crystal formation.*

The "family kinship" between the parent resolving agent (1-phenylethylamine) and the inhibitor is emphasized by the similarity of the bottom and left corner of the puzzle pieces in Figure 6.11. The nucleation inhibitor fits into the lattice to a certain extent; this means that the nature and the site of the (steric and electrostatic) interactions must be more or less the same.

When the nucleation inhibitor is adsorbed on layer **III** and the boundary of layer **II** reaches the site of inhibition, no further interactions are possible and the growth of layer **II** is inhibited. The difference between a regular impurity and a family member therefore must be that the interaction of binding to the surface is stronger because of the family kinship. Therefore the family member is adsorbed on the face longer than a regular impurity, so that it is still present during the formation of the next growth layer and thus hampers the crystallization most effectively. It is suggested that this inhibition takes place at the earliest stages of their development.

6.8 Conclusions

1-Phenylbutylamine **6.4** proved to be a potential family member of 1-phenylethylamine **6.2** in second generation Dutch Resolution of mandelic acid **6.1** as quantified by turbidity measurements (Chapter 6.2.1) and determination of the crystallization behaviour as a function of temperature (Chapter 6.2.3). The effect of inhibition is strongly pronounced on the *more soluble* diastereomeric salt; *id est,* the more soluble diastereomer is kept longer in solution by increasing the metastable zone width. Herein lies the success of Dutch Resolution; with correct temperature control, more opportunity for selective precipitation of the less soluble diastereomeric salt is achieved.

Although there is no clear relationship between structure and ability to act as a potential nucleation inhibitor, a few general conclusions could still be drawn from the screening process:

- Chirality seems to be necessary. Of the four additives without a stereogenic center, none of them did bring about any meaningful improvements in resolvability.
- Screening for suitable family members to enhance a resolution process can be done by screening the racemic additives. The racemates are only marginally less effective compared to the enantiopure family members with the same configuration as the parent resolving agent. Since in most cases racemic additives are more easily accessible (either commercially available or by synthesis), one could even decide to use racemic instead of enantiopure family members both in screening for inhibitory effects as well as practical application.
- The "wrong" enantiomer can also be a nucleation inhibitor, although in our observation less effectively so. Absolute stereochemistry is not an absolute off/on switch.
- Because there is no easy relationship between structure and ability to act as a potential nucleation inhibitor, for screening purposes the "top-5" additives have to go into a line-up for every substrate.

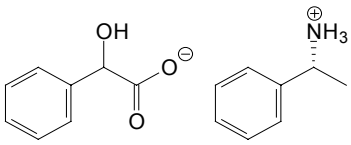
To prove that the enhancements are due to nucleation inhibition, as in the case of 1-phenylbutylamine, additional determination of the crystallization behaviour as a function of temperature or turbidity measurements could be performed.

6.9 Experimental Section

General information: For general remarks concerning all experimental details see experimental section in Chapter 3.

General procedure for the small scale second generation Dutch Resolution experiments described in Table 6.1. In a Kimble reactor tube (dimensions Ø 25 × 150 mm), provided with a cylindrical PTFE magnetic stirring bar (10 × 6 mm), a mixture of 0.20 mmol (0.10 mol equiv.) of additive **6.4**, 1.80 mmol of (*R*)-1-phenylethylamine **6.2** (0.90 mol equiv.) in 3.33 mL of *i*-propanol were mixed. Subsequently, 2.00 mmol racemic mandelic acid **6.1** (1.00 mol equiv.) in 1.67 mL of *i*-propanol was added. The mixture was heated until a clear solution was obtained. After the reactor tube was sealed with a rubber stopper, it was placed in the Varian thermostatted bath and the solution was mechanically stirred at 78 °C for 30 minutes. The tubes were gradually cooled to 20 °C with a ramp rate of –10 °C·h^{-1} and stirred at that temperature for 12 h. The precipitated salts were collected by filtration using the VacMaster®-20, each washed with 1.5 mL of *i*-propanol and dried.

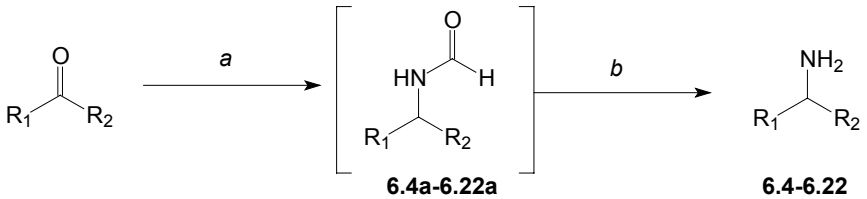
HPLC analysis of the salts was used to determine the diastereomeric excess of the salt. To ensure accurate *de* determination the racemic substrate was always measured first. The composition of the salt was determined by mass analysis, ^{1}H- and ^{13}C-NMR. The resolution experiments described in Table 6.5, Table 6.6, Table 6.7 and Table 6.9 were performed analogously to this general procedure with either 0.03 or 0.06 mol equiv. of additive (and respectively 0.97 or 0.94 mol equiv. of the parent resolving agent) with respect to the 1.00 mol equivalent of racemic substrate. The solvent(s) and concentration used are listed at the bottom of each table. The conditions for HPLC analysis for each substrate are given in section 6.9.1 of this experimental section. All experiments were performed in triplicate.



Less Soluble Salt of 6.1/6.2: (white salt). ^{1}H-NMR (200MHz, [D$_6$]DMSO): δ = 1.42 (d, J = 6.83 Hz, 3H), 4.27 (q, J = 6.83 Hz, 1H), 4.58 (s, 1H), 6.44 (brs, 3H, NH_3^+),7.12–7.49 (m, 10H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 20.08 (q), 48.77 (d), 42.47 (d), 125.11 (d), 125.27 (d), 125.61 (d), 126.36 (d), 126.96 (d), 127.49 (d), 139.26 (s), 142.47 (s), 174.09 (s) ppm. Anal. Calcd for $C_8H_8O_3 \cdot C_8H_{11}N$: C, 70.31 %; H, 7.01 %; N, 5.12 %. Found: C, 70.04 %; H, 7.03 %; N, 5.14 %.

Synthesis of the additives

The additives used in the screening for possible nucleation inhibitors, as described in section 6.3 of this chapter, were either commercially available (additives **6.9**, **6.10, 6.19** and **6.20**), synthesized as the racemic form by a simple one-pot Leuckart synthesis (additives **6.4**–**6.8**, **6.11**–**6.13**, **6.15**, **6.17**, **6.18**, **6.21** and **6.22**), or synthesized enantiopure by the three-step procedure described in Chapter 3 and 4 of this thesis (additives **6.4**, and **6.14**–**6.16**). In the first step of the Leuckart reductive amination reaction (Scheme 6.4), the intermediate formamides **6.4a**–**6.22a** are formed from the corresponding aldehydes or ketones. Without purification, the obtained intermediates are subsequently hydrolyzed with 10 % HCl to afford the racemic free amines **6.6**–**6.22** in good yields, which, if necessary, are purified by Kugelrohr distillation.

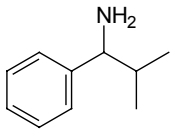


Scheme 6.4. *Leuckart synthesis of additives **6.4**–**6.8**, **6.11**–**6.13**, **6.15**, **6.17**, **6.18**, **6.21** and **6.22**. Reagents and conditions: (a) $HCONH_2$ / HCO_2H, Δ; (b) HCl, Δ.*

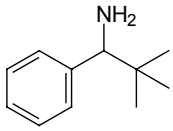
Note that in the cases of **6.12** and **6.13**, two stereocenters are present and a *meso* compound is possible. After the Leuckart reductive amination of the corresponding di-aldehydes, the reaction mixture contained a {(*R*,*R*)+(*S*,*S*)}:*meso* ratio of 85:15, according to ^{1}H-NMR analysis. After Kugelrohr distillation, the only products isolated were racemic **6.12** and **6.13** ({*(R,R)+(S,S)*}:*meso* > 99:1).

General procedure for the Leuckart synthesis of additives 6.4–6.8, 6.11–6.13, 6.15, 6.17, and 6.18. A mixture of the corresponding aldehyde or ketone (10 mmol), formamide (20 mL) and formic acid (10 mL) was heated to reflux. The mixture was refluxed for one hour. After cooling to ambient temperature, 30 mL of water was added and the mixture was extracted with diethylether (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to furnish the intermediate formamide. 20 mL aqueous HCl (30 %) was added and the reaction mixture was refluxed for one hour. After cooling to ambient temperature, 20 mL of water was added. The reaction mixture was carefully adjusted to pH 10 with aqueous NaOH (33 %) and extracted with diethylether (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to furnish the corresponding primary amines.

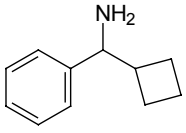
(±)-2-Methyl-1-phenyl-1-propanamine (6.6): (yellow oil, 83 % yield). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 0.72 (d, J = 6.59 Hz, 3H), 0.92 (d, J = 6.59 Hz, 3H), 1.41 (brs, 2H), 1.74–1.85 (m, 1H), 3.54 (d, J = 7.32 Hz, 1H), 7.17–7.28 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 18.81 (q), 19.70 (q), 35.36 (d), 62.37 (d), 128.03 (d), 126.91 (d), 128.03 (d), 150.91 (s) ppm. MS (CI): *m/z* = 150 [M + H$^+$].



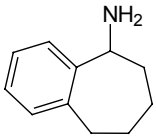
(±)-2,2-Dimethyl-1-phenyl-1-propanamine (6.7): (pale yellow oil, 95 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.86 (s, 9H), 1.40 (brs, 2H), 3.65 (s, 1H), 7.17–7.25 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 26.43 (q), 34.91 (s), 65.22 (d), 126.62 (d), 127.38 (d), 128.14 (d), 143.68 (s) ppm. MS (EI): *m/z* = 163 [M$^+$].



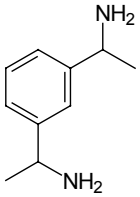
(±)-Cyclobutyl(phenyl)-methanamine (6.8): (orange oil, 61 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.39 (brs, 2H), 1.60–1.85 (m, 5H), 2.07–2.14 (m, 1H), 2.41–2.49 (m, 1H), 3.73 (d, J = 9.15 Hz, 1H), 7.15–7.28 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 17.41 (t), 25.33 (t), 26.04 (t), 43.21 (d), 61.64 (d), 126.51 (d), 126.77 (d), 128.17 (d), 144.70 (s) ppm. MS (CI): *m/z* = 162 [M + H$^+$].



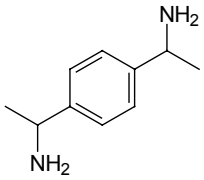
(±)-6,7,8,9-Tetrahydro-5*H*-benzo[*a*]cyclohepten-5-amine (6.11): (colorless liquid, 53 % yield after Kugelrohr distillation). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.52–2.02 (m + brs, 8H), 2.82–2.87 (m, 2H), 4.21–4.25 (m, 1H), 7.10–7.26 (m, 4H), 7.42–7.45 (m, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 27.42 (t), 28.69 (t), 35.67 (t), 37.11 (t), 54.60 (d), 124.00 (d), 126.00 (d), 126.19 (d), 129.28 (d), 141.25 (s), 145.57 (s) ppm. MS (EI): *m/z* = 161 [M^+].



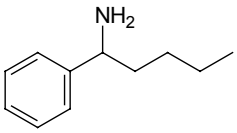
(±)-1-[3-(1-Aminoethyl)phenyl]-1-ethanamine (6.12): After workup the reaction mixture contained a *rac*:*meso* ratio of 85:15, according to ^{1}H-NMR analysis. After Kugelrohr distillation, the only product isolated was racemic **6.12** (*rac*:*meso* >99:1). (colorless oil, 53 % yield after Kugelrohr distillation). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.59 Hz, 6H), 2.63 (brs, 4H), 3.98 (q, *J* = 6.59 Hz, 2H), 7.07–7.17 (m, 4H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 25.07 (q), 49.64 (d), 122.85 (d), 124.10 (d), 128.60 (d), 147.29 (s) ppm. MS (CI): *m/z* = 165 [M + H^+].



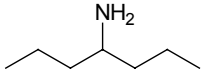
(±)-1-[4-(1-Aminoethyl)phenyl]-1-ethanamine (6.13): After workup the reaction mixture contained a *rac*:*meso* ratio of 80:20, according to ^{1}H-NMR analysis. After Kugelrohr distillation, the only product isolated was racemic **6.13** (*rac*:*meso* >99:1). (colorless oil, 47 % yield after Kugelrohr distillation). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.59 Hz, 6H), 1.51 (brs, 4H), 4.05 (q, *J* = 6.59 Hz, 2H), 7.26 (s, 4H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 25.50 (q), 50.82 (d), 125.60 (d), 146.16 (s) ppm. MS (CI): *m/z* = 165 [M + H^+].

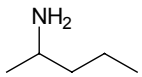


(±)-1-Phenyl-1-pentanamine (6.17): (yellow oil, 87 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.78 Hz, 3H), 1.06–1.27 (m, 4H), 1.41 (brs, 2H), 1.57–1.63 (m, 2H), 3.80 (t, *J* = 6.78 Hz, 1H), 7.13–7.31 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.79 (q), 22.46 (t), 28.55 (t), 39.21 (t), 56.08 (d), 126.07 (d), 126.54 (d), 128.14 (d), 146.69 (s) ppm. MS (EI): *m/z* = 163 [M^+].



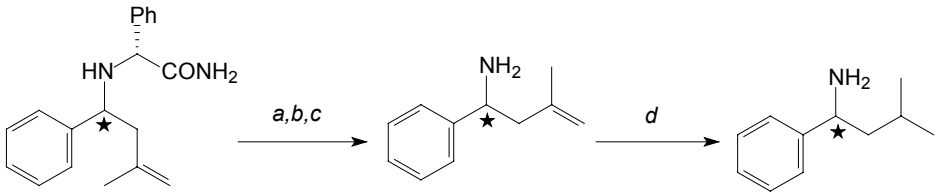
(±)-1-Propylbutylamine (6.21): (colorless liquid, 55 % yield after Kugelrohr distillation). ^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.75–0.80 (m, 6H), 1.17–1.36 (m, 8H), 2.78 (t, *J* = 5.32 Hz, 1H), 5.02 (brs, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.76 (q), 18.50 (t), 37.50 (t), 51.71 (d) ppm. MS (CI): *m/z* = 116 [M + H^+].





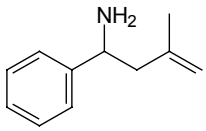
(±)-1-Methylbutylamine (6.22): (colorless oil, 65 % yield after Kugelrohr distillation). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 0.81–0.88 (m, 3H), 0.98 (d, J = 6.34 Hz, 3H), 1.10–1.39 (m, 4H), 1.63 (brs, 2H), 2.77–2.86 (m, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.86 (q), 19.29 (t), 23.63 (q), 42.18 (t), 46.37 (d) ppm. MS (EI): m/z = 88 [M^+].

Additive **6.15** was obtained by subjecting PGA methallylamine **3.62** to the non-reductive removal of the PGA moiety as described in Chapter 4 of this thesis (Scheme 6.5, step *a–c*). The saturated counterpart, additive **6.16** could be obtained by subsequent reduction of the allylic double bond of **6.15** using H_2 and 10 % palladium on carbon (step *d*). Racemic **6.16** was obtained by reductive amination (Leuckart) of isovalerophenone.[22]

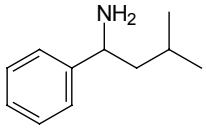


3.62 **6.15** **6.16**

Scheme 6.5. *Synthesis of enantiopure additives **6.15** and **6.16**.*

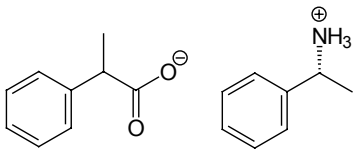


3-Methyl-1-phenyl-3-butenylamine (6.15): (pale yellow liquid, 47 % over 3 steps). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.75–1.79 (m, 3H), 2.33–2.44 (m, 2H), 2.59–2.70 (m + brs, 4H), 4.21 (dd, J = 7.85, J = 5.24 Hz, 1H), 7.05–7.31 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 24.21 (q), 43.45 (t), 54.00 (d), 120.37 (t), 125.95 (d), 128.40 (d), 128.66 (d), 141.58 (s), 145.74 (s) ppm. MS (CI): m/z = 162 [M + H^+].

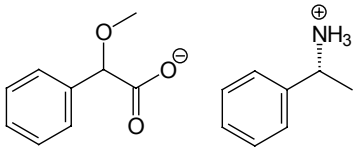


3-Methyl-1-phenylbutylamine (6.16): (colorless liquid, 95 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.86–0.90 (m, 6H), 1.44 (brs, 2H), 1.49–1.55 (m ,3H), 3.90 (t, J = 6.41 Hz, 1H), 7.12–7.33 (m, 5H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 22.38 (q), 24.96 (d), 48.36 (t), 53.96 (d), 126.14 (d), 126.67 (d), 128.32 (d), 147.00 (s) ppm. MS (CI): m/z = 164 [M + H^+].

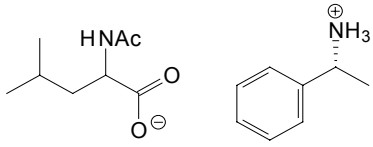
Less Soluble Salt of 6.23/6.2: ^{1}H-NMR (200MHz, [D$_6$]DMSO): δ = 1.31 (d, J = 7.32 Hz, 3H), 1.37 (d, J = 6.60 Hz, 3H), 3.50 (q, J = 7.32 Hz, 1H), 4.15 (q, J = 6.60 Hz, 1H), 5.12 (brs, 3H, NH_3^+), 7.16-7.32 (m, 6H), 7.36 (d, J = 7.32 Hz, 2H), 7.43 (d, J = 8.05 Hz, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 19.45 (q), 23.12 (q), 46.99 (d), 50.02 (d), 125.80 (d), 126.33 (d), 127.24 (d), 127.45 (d), 127.92 (d), 128.30 (d), 143.76 (s), 176.68 (s) ppm. Anal. calcd for $C_9H_{10}NO_2 \cdot C_8H_{11}N$: C, 75.25 %; H, 7.80 %; N, 5.16 %. Found: C, 75.40 %; H, 7.87 %; N, 5.15 %.



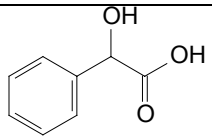
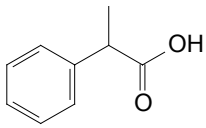
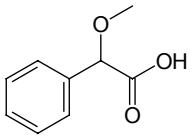
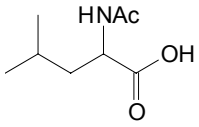
Less Soluble Salt of 6.24/6.2: ^{1}H-NMR (200MHz, [D$_6$]DMSO): δ = 1.36 (d, J = 7.32 Hz, 3H), 3.21 (d, J = 2.20, 3H), 4.18 (q, J = 7.32 Hz), 4.89 (d, J = 2.20, 1H), 7.19-7.44 (m, 10H) ppm. ^{13}C-NMR (50MHz, [D$_6$]DMSO): δ = 21.00 (q), 48.83 (q), 55.13 (q), 55.13 (d), 83.54 (d), 125.49 (d), 125.75 (d), 125.85 (d), 126.54 (d), 127.36 (d), 139.23 (d), 139.23 (s), 140.86 (s), 171.81 (s) ppm. Anal. calcd for $C_9H_{10}O_3 \cdot C_8H_{11}N$: C, 71.06 %; H, 7.37 %; N, 4.87 %. Found: C, 70.93 %; H, 7.31 %; N, 4.75 %.



Less Soluble Salt of 6.24/6.2: ^{1}H-NMR (200MHz, [D$_6$]DMSO): δ = 0.83–0.88 (m, 6H), 1.39 (d, J = 6.95 Hz, 2H), 1.43–1.68 (m, 2H), 1.82 (s, 3H), 4.08 (q, J = 6.95 Hz, 1H), 4.20 (q, 1H, J = 6.47 Hz, 1H), 4.81 (brs, 3H, NH_3^+), 7.26-7.46 (m, 4H), 7.70 (d, J = 8.06 Hz, 1H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 21.84 (q), 22.66 (q), 23.07 (q), 24.43 (d), 41.51 (t), 50.05 (d), 51.67 (d), 128.34 (d), 127.29 (d), 126.32 (d), 143.64 (s), 168.44 (s), 175.05 (s) ppm. Anal. calcd for $C_8H_{15}NO_3 \cdot C_8H_{11}N$: C, 65.28 %; H, 8.90 %; N, 9.52 %. Found: C, 65.20 %; H, 8.90 %; N, 9.46 %.



Conditions for HPLC Analysis

Entry	Substrate	HPLC column	Conditions	Ret. Times (min.)
1	 (±)-**6.1**	Chiralpak AD	hexane:*i*-propanol:TFA (90:10:0.1) 1.0 mL·min^{-1}	21.0 (*R*) 25.0 (*S*) (at λ = 220 nm)
2	 (±)-**6.23**	Chiralcel OB	heptane:ethanol:TFA (99:1:0.2) 1.0 mL·min^{-1}	40.2 (*S*) 56.5 (*R*) (at λ = 210 nm)
3	 (±)-**6.24**	Chiralcel AS-RH	25 mM KH_2PO_4 buffer (*p*H=2): acetonitrile (92:8) 0.3 mL·min^{-1}	35.7 (*S*) 38.9 (*R*) (at λ = 205 nm)
4	 (±)-**6.24**	Chirobiotic T	methanol:acetic acid:TEA (99.5:0.1:0.1) 1.0 mL·min^{-1}	4.4 (*S*) 18.4 (*R*) (at λ = 210 nm)

6.10 References

[1] [1a] T. R. Vries, H. Wynberg, E. van Echten, J. Koek, W. ten Hoeve, R. M. Kellogg, Q. B. Broxterman, A. Minnaard, B. Kaptein, S. van der Sluis, L. A. Hulshof and J. Kooistra, *Angew. Chem. Int. Ed.* **1998**, *37*, 2349–2354. [1b] Eur. Pat. Appl. EP 0,838,448 (to DSM).

[2] [2a] J. W. Nieuwenhuijzen, R. F. P. Grimbergen, C. Koopman, R. M. Kellogg, T. R. Vries, K. Pouwer, E. van Echten, B. Kaptein, L. A. Hulshof and Q. B. Broxterman, *Angew. Chem. Int. Ed.* **2002**, *41*, 4281–4286. [2b] J. W. Nieuwenhuijzen, *Resolutions with Families of Resolving Agents: Principles and Practice*; Ph. D. Thesis, University of Groningen, The Netherlands, **2002**. [2c] R. M. Kellogg, J. W. Nieuwenhuijzen,

K. Pouwer, T. R. Vries, Q. B. Broxterman, R. F. P. Grimbergen, B. Kaptein, R. M. La Crois, E. de Wever, K. Zwaagstra and A. C. van der Laan, *Synthesis* **2003**, 1626–1638.

[3] The S-factor is a measure for the resolution efficiency and is described in Chapter 1.6.2 of this thesis.

[4] According to HPLC, mass analysis, ^{1}H- and ^{13}C-NMR.

[5] Experimental details can be found in Chapter 3 of this thesis.

[6] Reproducibilities are good and all values reported are mean values from at least three experiments; the experimentally determined error limit of the S-factor is ± 5%.

[7] The conditions and chiral HPLC-columns used for analysis are reported in the experimental section.

[8] To reduce the amount of data, the computer records one data point per minute.

[9] Concentration of the more soluble diastereomeric salt used in the turbidity measurements is 1.58 mmol·mL^{-1} *i*-propanol.

[10] See also Chapter 2 of this thesis.

[11] Concentration of the less soluble diastereomeric salt used in the turbidity measurements is 0.12 mmol·mL^{-1} *i*-propanol.

[12] Since the concentration in the turbidity measurements with the *more* soluble salts are much higher than in the measurements with the *less* soluble salts, the margins of error are probably somewhat larger than in the latter.

[13] A 1:1:1 mixture of enantiopure **6.2**, **6.5** and **6.6** has been used in the past (ref. [1a]) as a family of resolving agents ("PE-III mix").

[14] [14a] L. Addadi, Z. Berkovitch–Yellin, N. Domb, E. Gati, M. Lahav and L. Leiserowitz, *Nature* **1982**, *296*, 21–26. [14b] Z. Berkovitch–Yellin, L. Addadi, M. Idelson, L. Leiserowitz and M. Lahav, *Nature* **1982**, *296*, 27–34. [14c] K. Sakai, Y. Maekawa, K. Saigo, M. Sukegawa, H. Murakami and H. Nohira, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1747–1750.

[15] For preparation of a sample for HPLC-analysis simply 0.5 mg of the salt was dissolved in 10 mL *i*-propanol.

[16] [16a] P. Bravo, E. Piovosi, G. Resnati and G. Fronza, *J. Org. Chem*. **1989**, *54*, 5151–5176. [16b] P. Bravo, F. Ganazzoli, G. Resnati, S. de Munari and A. Albinati, *J. Chem. Res.* **1988**, 216–217. [16c] M. Raban and K. Mislow, *Tetrahedron Lett.* **1977**, *18*, 1527–1531.

[17] G. Helmchen, H. Volter and W. Schule, *Tetrahedron Lett.* **1977**, *18*, 1417–1420.

[18] G. Helmchen and R. Schmierer, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 703–704.

[19] [19a] D. Valentine Jr., K. K. Johnson, W. Priester, R. C. Sun, K. Toth and G. Saucy, *J. Org. Chem.* **1980**, *45*, 3698–3703. [19b] R. Garcia, J. M. Seco, S. A. Vazquez, E. Quinoa and R. Riguera, *J. Org. Chem.* **2002**, *67*, 4579–4589. [19c] P.H. Buist, B. Behrouzian, S. Cassel, C. Lorin, P. Rollin, A. Imberty and S. Perez, *Tetrahedron: Asymmetry* **1997**, *8*, 1959–1961.

[20] B. M. Trost and D. P. Curran, *Tetrahedron Lett.* **1981**, *22*, 4929–4932.

[21] T. Ichiba, T. Murashi, T. Ohtsuka and M. Masuko, *J. Pestic. Sci.* **2002**, *27*, 118–126.

[22] The IUPAC name of isovalerophenone is 3-methyl-1-phenyl-1-butanone.

Chapter 7
Epilogue and Future Prospects

In this epilogue the leads and prospects for second generation Dutch Resolution experiments are discussed. Because some of the unexpectedly high inhibitory effects were achieved with additives that bear two amino groups in their structure, suggestions are made for other multifunctional resolving agents. Preliminary results of the work on these new compounds are evaluated in this chapter. Furthermore, some recommendations for future research on 'high-throughput screening' of (Dutch) resolution experiments are presented.

Part of this chapter will be submitted for publication in *Angew. Chem. Int. Ed.*: J. Dalmolen, T. D. Tiemersma-Wegman, J. W. Nieuwenhuijzen, M. van der Sluis, B. Kaptein, R. M. Kellogg and Q. B. Broxterman.

7.1 Diamino Structures

7.1.1 (Possible) Synthesis of New Diamino Structures

For all racemates described in Chapter 6 that were subjected to the second generation Dutch Resolution protocol, in every case at least one of the (racemic) diamino additives **6.12** and **6.13** showed by far the largest nucleation inhibitory effect. In two cases even *both* **6.12** and **6.13** gave the largest improvement in the resolution efficiency. One must also keep in mind that we only screened at *two* concentrations of the diamino additives (3 and 6 mol %) and that the optimal concentration of additives was not determined.

Both the generally applicable synthetic routes based on chirality transfer by (*R*)-PGA (described in Chapter 3 and 4 of this thesis) might give easy excess to another class of dimeric structures (Figure 7.1). Since **6.12** and **6.13** were strikingly effective as nucleation inhibitors, unsaturated butenyl-derivatives **7.1**–**7.3** and saturated butyl-derivatives **7.4**–**7.6** are, both for reasons of structural analogy and potential synthetic availability, interesting to screen for nucleation inhibitory effects.

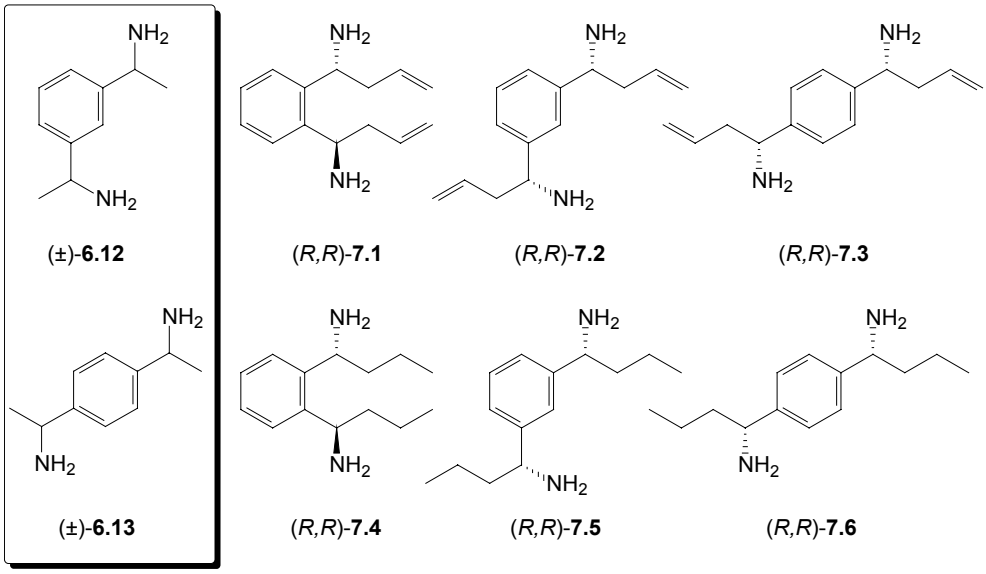
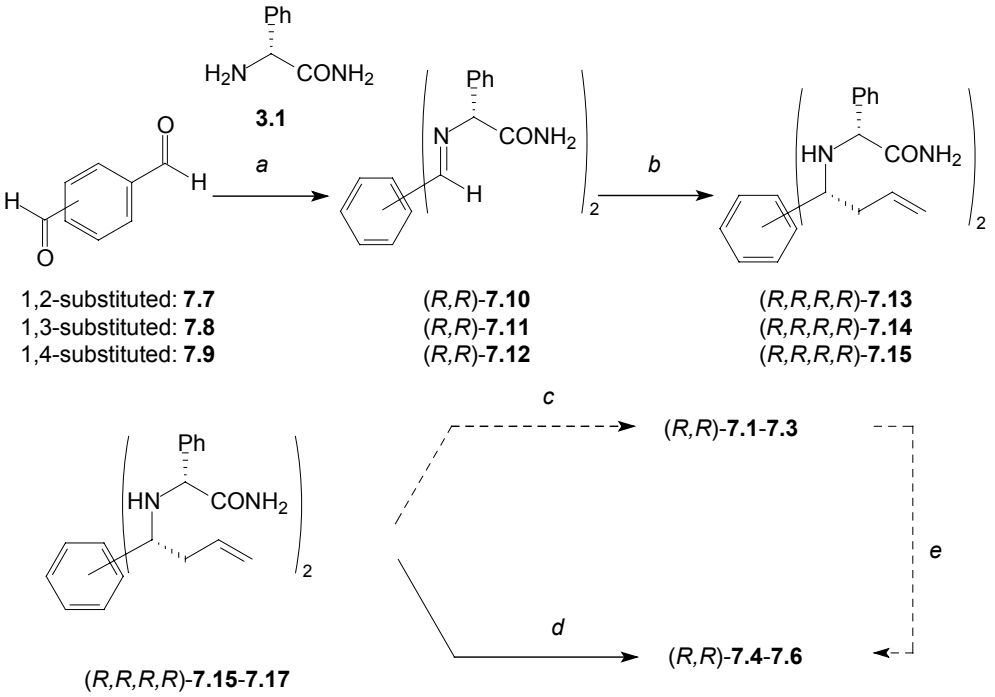


Figure 7.1 *Possible new diamino structures **7.4**–**7.6**.*

PGA imines **7.11** and **7.12** (Scheme 7.1) could be obtained starting from respectively the 1,3-substituted benzenedicarboxaldehyde **7.8** (isophthalaldehyde) or 1,4-substituted benzene dicarboxaldehyde **7.9** (terephthalaldehyde) in excellent yields (Table 7.1). Unfortunately, reaction between (*R*)-PGA **3.1** (2 equiv.) and 1,2-substituted benzenedicarboxaldehyde **7.7** (phthaldehyde) failed to produce the corresponding imine

7.10. A complex mixture of products, including starting material, was observed by NMR spectroscopy.



Scheme 7.1 *Synthetic strategy to dimeric structures (R,R)-**7.1**–**7.6**. Reagents and conditions: (a) (R)-PGA (**3.1**), CH_2Cl_2, rt; (b) allylzinc bromide ([CH_2=$CHCH_2ZnBr$], 1.5 equiv.), THF, 0 °C to rt; (c) non-reductive removal of the (R)-PGA auxiliary (as described in Chapter 4); (d) AcOH/H_2O/ i-propanol, H_2, Pd-C (10 %); (e) reduction of the allylic moiety with H_2 and Pt-C.*

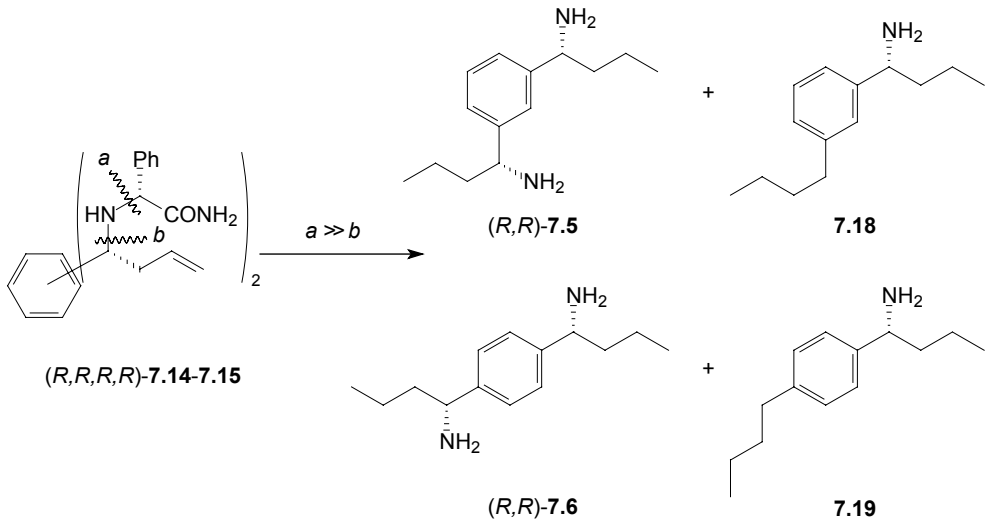
Table 7.1 *Synthesis of allylamines **7.14** and **7.15** by formation of imines **7.11** and **7.12** followed by allylation.*

Entry	Imine	Yield (%)[a]	Allylamine	Yield (%)[a]	*dr* (*R*,*R*):(*R*,*S*)[b]
1	**7.10**	–[c]	**7.13**	–	–
2	**7.11**	96	**7.14**	99	>99:1
3	**7.12**	98	**7.15**	99	>99:1

[a] Isolated yield. [b] Diastereomeric ratios were determined with ^{1}H-NMR spectroscopy. [c] Failed to produce corresponding imine.

Subsequent addition of imines (*R*,*R*)-**7.11** and (*R*,*R*)-**7.12** to preformed allylzinc bromide (3 equiv.) in THF at 0 °C afforded the (*R*,*R*,*R*,*R*)-PGA allylamines **7.14** and **7.15** in quantitative yields and excellent diastereoselectivities (Table 7.1).

Reductive removal of the PGA auxiliary by catalytic hydrogenation of allylamines **7.14** and **7.15** is hardly more complicated than the regioselective removal of 'di-*N*-benzylic' PGA allylamines described in Chapter 3.4. Assuming that cleavage according to route *a* is by far favoured over route *b* (Scheme 7.2), in theory two possible products can be found in the reaction mixture. One is the desired "free" primary diamino structure (*R*,*R*)-**7.5** or (*R*,*R*)-**7.6** and the other is the by-product **7.18** or **7.19**, respectively.



Scheme 7.2 *Selectivity of cleavage in the reductive removal of the PGA moiety by catalytic hydrogenation. Reagents and conditions: i-propanol/H_2O/AcOH, H_2, Pd-C (10 %).*

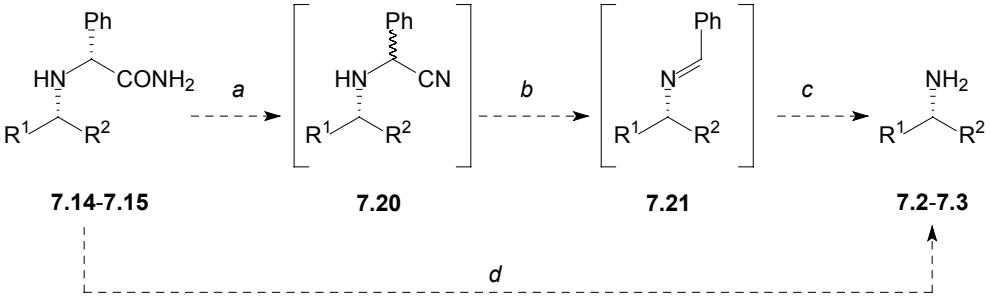
The selectivities (*a*:*b*) towards products **7.5**–**7.6** were determined by ^{1}H-NMR spectroscopy, analogously to the approach described in Chapter 3.4. As assumed, both PGA allylamines **7.14** and **7.15** showed pleasingly high selectivities in cleavage of the C-N bond via route *a*. The free primary diamines **7.5** and **7.6** were obtained in satisfactory yields and regioselectivities of cleavage up to 97:3, depending on site of substitution (Table 7.2). The (*R*)-configuration at both stereocenters is assigned by analogy from our work on chirality transfer of (*R*)-PGA described in Chapter 3 of this thesis but has not been verified explicitly.

Table 7.2 *Regioselective cleavage of the chiral auxiliary and generation of diamines **7.5** and **7.6** by catalytic hydrogenation.*

Entry	Allylamine	Butylamine	Yield (%)[a]	Selectivity *a*:*b* [b]
1	**7.14**	**7.5**	80	95:5
2	**7.15**	**7.6**	74	97:3

[a] Isolated yield. [b] Regioselectivity values were determined with ^{1}H-NMR spectroscopy.

Recently, a novel one-pot procedure for the non-reductive removal of PGA-auxiliaries became available (Scheme 7.3, route *d*).[1] This elegant one-pot procedure was used in the synthesis of (*S*)-1-aminoindane, a key building block in the preparation of some pharmaceutically important therapeutic agents. As an alternative to the non-reductive removal described in Chapter 4 of this thesis (Scheme 7.3, route *a–c*), where intermediates **7.20** and **7.21** are isolated, this alternative route might be worth investigating. Although this one-pot procedure has been used to synthesize some of the butenylamines from Chapter 4 on a large scale (0.5–1.0 mol),[‡] we have not had the opportunity to try this route in the laboratory for the preparation of additives **7.2** and **7.3**.



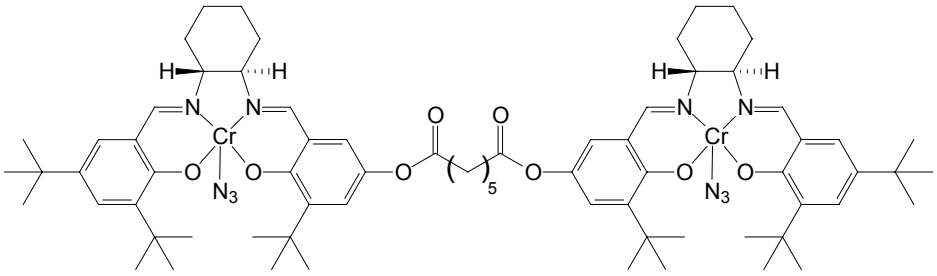
Scheme 7.3 *Non-reductive chiral auxiliary removal. Reagents and conditions: (a) Vilsmeier reagent [ClCH=N(CH$_3$)$_2$$^+Cl^-$], CH$_2Cl_2$, NEt$_3$, 0 °C to rt; (b) K$_2CO_3$, EtOH, reflux, 2h; (c) NH$_2$OH.HCl, THF/H$_2$O, rt; (d) POCl$_3$, Et$_3$N, THF, 0°C to reflux; NH$_2$OH·HCl, H$_2$O.*

7.2 Polyfunctional Resolving Agents

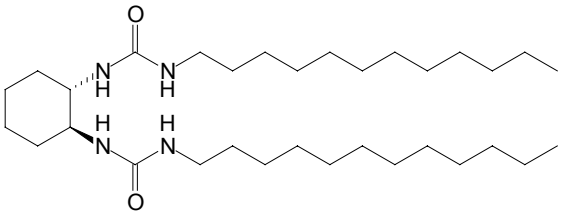
A general phenomenon often observed in chemistry is that molecules that possess repeating functionalities in their structure have a greater tendency to aggregate. Examples from widely diverse fields are (a) dimeric catalysts like **7.22**,[2] which showed enhanced activity,

[‡] *Unpublished results.*

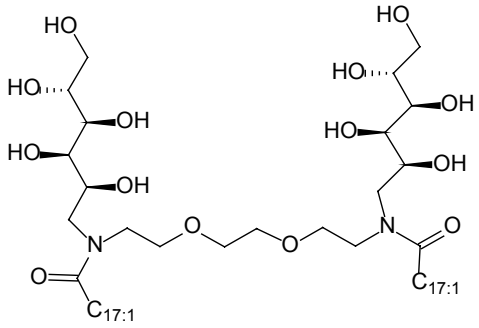
compared to the monomeric analogues; (b) bis-urea based compounds like **7.23** developed in Groningen,[3] which undergo highly selective aggregation to form organic gels; and (c) amide-containing sugar-based gemini surfactants, also developed in Groningen,[4] which exhibit a remarkable tendency to form micelles or vesicles (depending on the pH value).



7.22



7.23



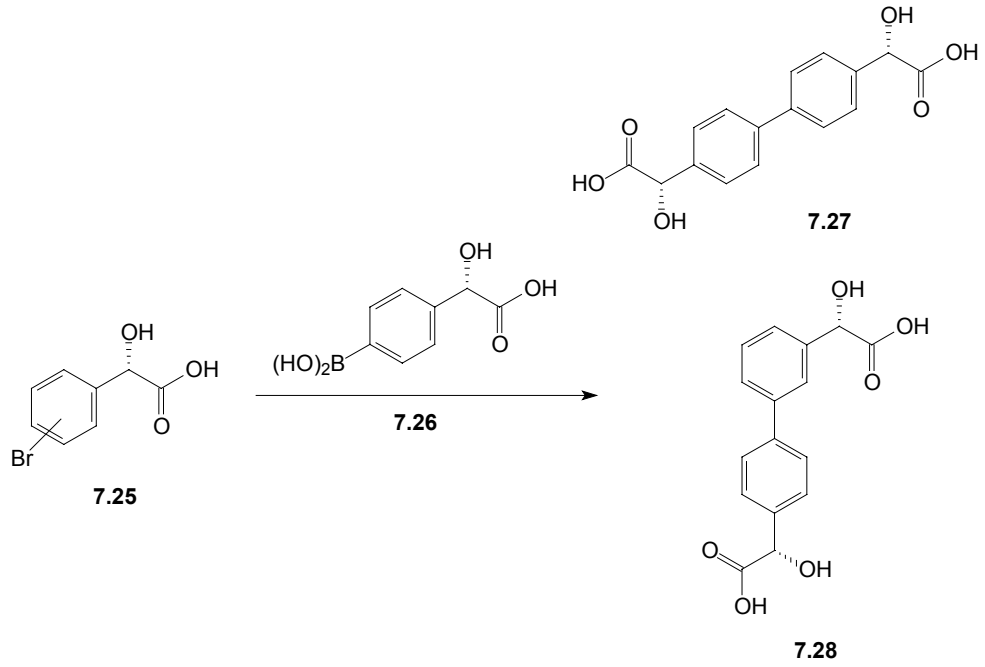
7.24

Figure 7.2 *Examples of molecules with a great tendency to form aggregates.*

Polyfunctional resolving agents could perhaps exhibit similar tendencies to aggregate and induce rapid precipitation. Polyfunctional **7.5** and **7.6** could be interesting potential resolving agents, either independently or as new family members of two in second

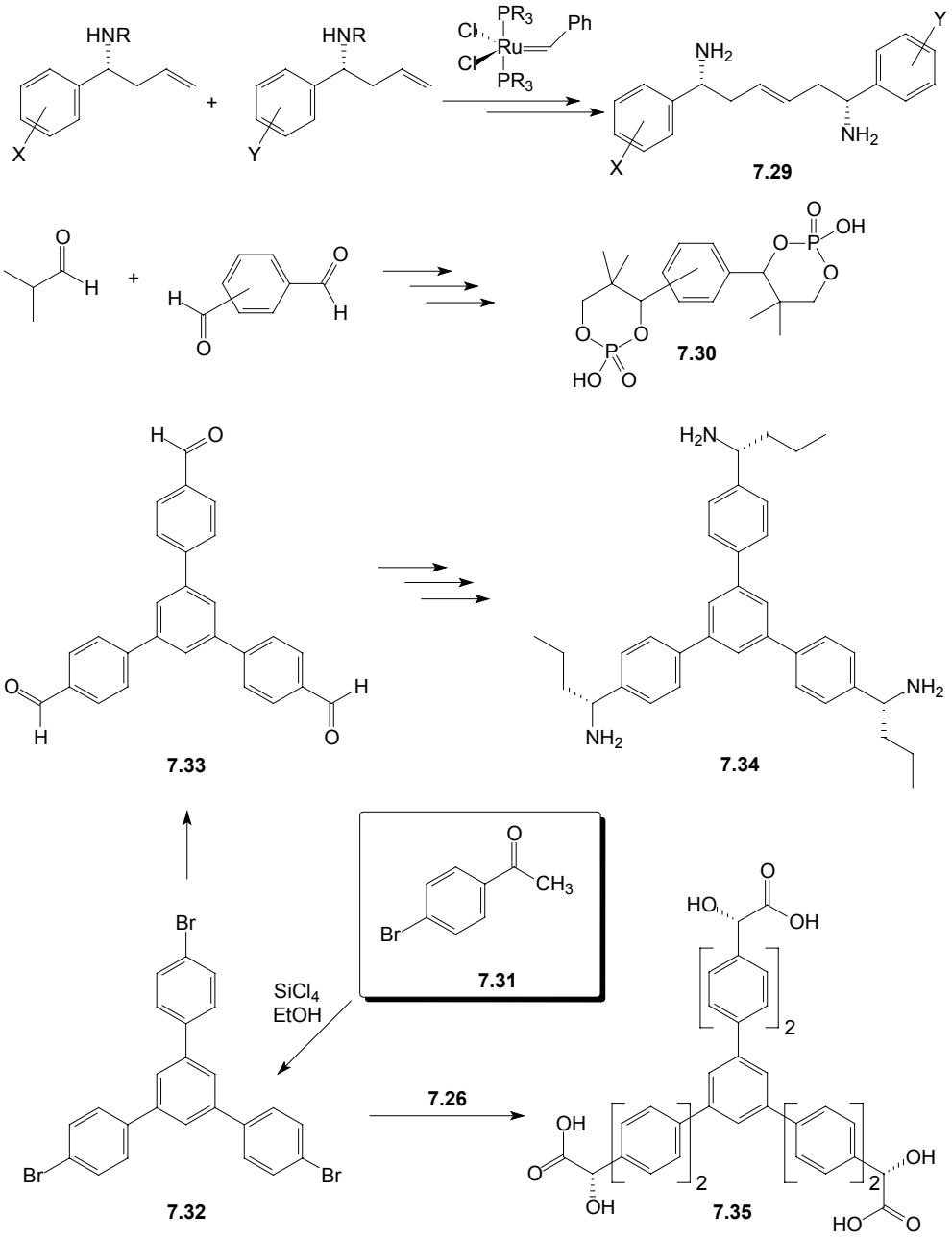
generation Dutch Resolution experiments. The same holds for dimeric structures **7.2** and **7.3**.

How could one obtain new polyfunctional acidic resolving agents? Cross coupling reactions may be used to prepare the highly interesting dimeric mandelic acids depicted in Scheme 7.4. Dimers **7.27** and **7.28** could be accessible via a Suzuki[5] coupling of the 1,3- or 1,4-bromo-substituted mandelic acid **7.25** and boronic acid **7.26.** Worth trying is the methodology reported by Dyer *et al.*, which used the relatively inexpensive palladium on carbon as the catalyst and has been used in the preparation of resolving agents based on 4-arylmandelic acids.[6] Other cross-coupling strategies are also possible.[7,8] The mixed dimers **7.27** and **7.28** are in fact a "two-component family".



Scheme 7.4 *Strategies for preparation of dimeric acids **7.27** and **7.28**.*

More complex polyfunctional resolving agents can be designed by going to, for example, molecules with three functional groups. Many polyfunctional resolving agents can readily be imagined (Scheme 7.5). Several combinations involving metathesis reactions can be envisioned,[9] a simple example is hexene-diamine **7.29**. Dimeric (or trimeric) cyclic phosphoric acids **7.30** could be accessible by the straightforward synthesis developed by Wynberg *et al*.[10]



Scheme 7.5 *Possible strategies for the preparation of compound **7.29**, **7.30**, **7.34** and **7.35**.*

Tribromide **7.32**, could be a important building block in both the synthesis of enantiopure triamine **7.34** and triacid **7.35**, and can easily be obtained on a 40 grams scale via a $SiCl_4$-catalyzed repetitive condensation reaction of *para*-bromoacetophenone **7.31**.[11,] Trialdehyde **7.33** could then be synthesized by formylation of **7.32**[12] and subsequently subjected to the chirality transfer approach described in this thesis to obtain (*R*,*R*,*R*)-**7.34**. Synthesis of triacid **7.35** might be achieved by a Suzuki coupling of **7.32** and boronic acid **7.26**.

One should keep in mind that resolving agents must in general be available in multigram quantities and that the synthesis of these compounds must be scaled-up to multi-kilogram scale to become industrially applicable. The advantage of the second generation Dutch Resolution protocol is that the additive is only added in more 'catalytic' amounts (< 10 mol %). Therefore the polyfunctional resolving agents shown in Scheme 7.4 and Scheme 7.5 might also be tested as additives in a potential family; for instance, (racemic) dimer **7.30** can be tested as possible nucleation inhibitor in resolutions with phencyphos **4.65** as the parent resolving agent.

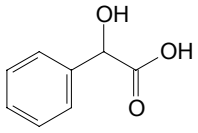
7.3 New Diamino Structures as Additives

In view of the promising results obtained with diamino additives **6.12** and **6.13** as nucleation inhibitors, we decided to screen both new diamino structures **7.5** and **7.6** as additives in the second generation Dutch Resolution with (*R*)-1-phenylethylamine **6.2** as parent resolving agent (Table 7.3). In three of the four substrates tested, at least one of the two diamine additives gave a considerable improvement in resolution efficiency. Only in the resolution of α-methoxyphenylacetic acid **6.24** no "hits" (S > 0.35) were found on addition of either **7.5** or **7.6**. Of the other substrates, only a few cases will be highlighted.

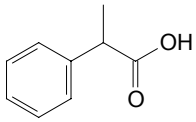
In the resolution of mandelic acid **6.1**, additive **7.5** at least matches the results obtained with diamino additives **6.12** and **6.13**. The addition of 3 mol % or 6 mol % of **7.5** both gave comparable results, the *de* of the first salts increases from 14 % to 46–48 % *de* resulting in an increase in S-factor from 0.19 to 0.47–0.52 (Table 7.3, entries 2^a and 2^b). Diamino additive **7.6** even exceeded the results obtained so far with all other additives screened in the resolution of mandelic acid. On addition of 6 mol % of **7.6** the *de* increased to a satisfying 67 % resulting in an increase in S-factor from 0.19 to 0.82 (entry 3^b).

In the resolution of hydratropic acid **6.23,** maybe not the greatest enhancement in resolution efficiencies were obtained on using **7.5** and **7.6** as additives, but **7.6** showed the strongest nucleation inhibitory effect observed up until now (entry 5). A dramatic effect was observed on addition of 3 mol % of **7.6**, as the yield of the first salts is dropped significantly, the *de* is raised to an astonishing 86 % (S-factor of 0.44). The effect becomes even stronger on addition of 6 mol % of **7.6** (entry 5^b), instead of a salt with essentially no diastereoselectivity, a salt is obtained in a yield of 18 % but with a *de* of 97 %. The general conclusion that can be drawn from the results in Table 7.3 is that additives **7.5** and **7.6** are potential new family members of 1-phenylethylamine **6.2**.

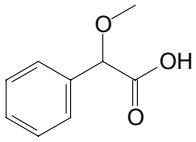
Table 7.3 *Racemates screened in resolution experiments with **7.5** and **7.6** as additives.*



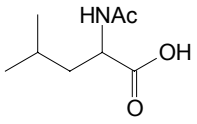
6.1



6.23



6.24



6.25

Entry	Racemic Acid	Additive	Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[c]
1	**6.1**	–	–	68	14	0.19
2[a]	**6.1**	(*R*,*R*)-**7.5**	3	54	48	0.52
2[b]			6	51	46	0.47
3[a]	**6.1**	(*R*,*R*)-**7.6**	3	63	44	0.56
3[b]			6	61	67	0.82
4	**6.23**	–	–	60	7	0.08
5[a]	**6.23**	(*R*,*R*)-**7.5**	3	25	86	0.44
5[b]			6	18	97	0.35
6[a]	**6.23**	(*R*,*R*)-**7.6**	3	44	26	0.23
6[b]			6	50	21	0.21
7	**6.24**	–	–	65	1	0.02
8[a]	**6.24**	(*R*,*R*)-**7.5**	3	53	28	0.30
8[b]			6	53	26	0.28
9[a]	**6.24**	(*R*,*R*)-**7.6**	3	19	40	0.15
9[b]			6	11	56	0.12
10	**6.25**	–	–	58	13	0.15
11[a]	**6.25**	(*R*,*R*)-**7.5**	3	44	48	0.43
11[b]			6	52	42	0.44
12[a]	**6.25**	(*R*,*R*)-**7.6**	3	51	29	0.30
12[b]			6	56	32	0.36

Experimental conditions for each substrate are given in Chapter 6.9. [a] Isolated yield of the first salts.[b] *de* of the first isolated salts. [d] S = 2 × yield × *de*.

Therefore these diamino additives have to be added to the "line-up of usual suspects", the top 5 additives from Chapter 6, in screening resolutions with 1-phenylethylamine as the resolving agents.

7.4 Bis-amines as Potential Family Members

So far we have only looked at primary amines as potential family members with variations on the aromatic ring, different ring structure or variations in the alkyl chain. Another possibility is to synthesize secondary amines or dimeric derivatives of a parent resolving agent.

In 1992, Sakai *et al.* reported the use of a dimeric bis-amine as a growth inhibitor to overcome an undesired crystal habit.[13] In the recrystallization of the less soluble salt of mandelic acid/1-phenylethylamine **6.1**/**6.2** he added bis-amine **7.36**, which in structure closely resembles 1-phenylethylamine **6.2**. In the presence of 0.05 mol % of bis-amine **7.36** with the same (*R*)-configuration at both stereogenic centers as the 1-phenylethylamine counterpart, the shape of the crystals changed from elongated plates (Figure 7.3a) into more hexagonal plates (Figure 7.3b). As can be seen from Figure 7.3c–d, the effect on habit modification strongly depended on the stereochemistry of the additives: (*R*,*S*)-**7.36** and (*S*,*S*)-**7.36** did not cause habit modification.

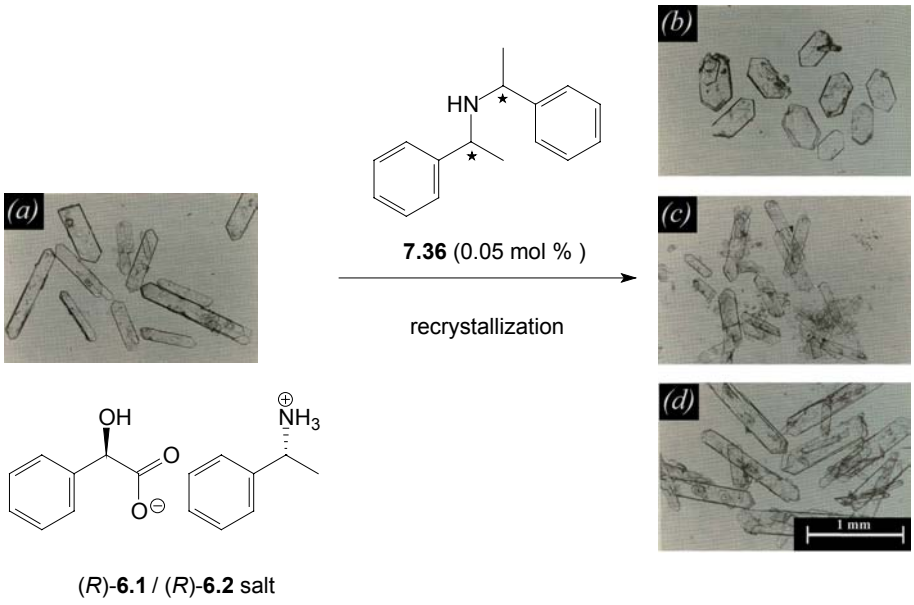


Figure 7.3 *Crystals of (R)-**6.1**/(R)-**6.2** grown (a) in the absence of **7.36** and in the presence of 0.05 mol % of (b) (R,R)-**7.36**, (c) (R,S)-**7.36** and (d) (S,S)-**7.36**.*[13]

To our knowledge **7.36** has never been used as a potential family member to induce nucleation inhibitory effects in resolution experiments (or even not as a resolving agent). Since bis-amine **7.36** is commercially available (in both enantiomeric forms), we decided to test racemic substrates **6.1**, **6.23**–**6.25** in resolution experiments with (*S*)-1-phenylethylamine **6.2** in the absence or presence of 6 mol % of (*S*,*S*)-**7.36**. The results are presented in Table 7.4.

Table 7.4 *Dutch resolution of racemic acids in the absence or presence of bis-amine **7.36**.*

Entry	Racemic Acid	Resolving Agent	Additive	Yield (%)[a]	*de* (%)[b]	S-Factor[c]
1	**6.1**	(*S*)-PEA	–	68	14	0.19
2	**6.1**	(*S*)-PEA	6 % (*S*,*S*)-**7.36**	44	29	0.26
3	**6.23**	(*S*)-PEA	–	60	7	0.08
4	**6.23**	(*S*)-PEA	6 % (*S*,*S*)-**7.36**	63	33	0.41
5	**6.24**	(*S*)-PEA	–	65	1	0.02
6	**6.24**	(*S*)-PEA	6 % (*S*,*S*)-**7.36**	51	29	0.30
7	**6.25**	(*S*)-PEA	–	58	13	0.15
8	**6.25**	(*S*)-PEA	6 % (*S*,*S*)-**7.36**	46	35	0.32

Experimental conditions for each substrate are given in Chapter 6.9. [a] Isolated yield of the first salts.[b] *de* of the first isolated salts. [d] S = 2 × yield × *de*.

Results with 6 mol % of bis-amine **7.36** were, however, not remarkable compared to results obtained with, for instance, the diamino additives. Only in the resolution of hydratropic acid **6.23**, the addition of 6 mol % of resulted in an S-Factor > 0.35 (Table 7.4, entry 4).

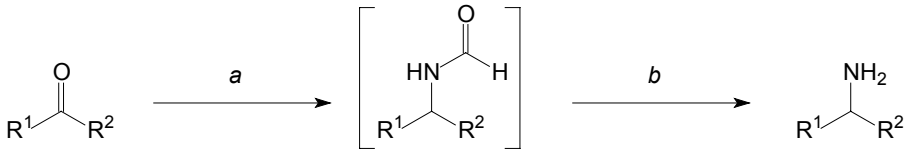
7.5 High Throughput Screening in Dutch Resolution Experiments

Recently, de Vries *et al.* published a description of the use of high-throughput synthesis and screening of libraries of ligands in homogeneous catalysis.[14] To our knowledge, the number of reports regarding the use of high-throughput screening in the field of resolutions are limited,[15,16] and there has certainly been no mention of the synthesis of possible family members of resolving agents and their subsequent screening.

De Vries *et al.*[14] state that the essentials for high-throughput experimentation (HTE) are:

- Hardware / robots (*e.g.* the Chemspeed's ASW 2000),
- Software and data handling,
- The right mindset,
- Libraries of ligands and catalysts (in our case libraries of easy accessible potential family members of resolving agents), and
- Fast analysis.

Our work described in Chapter 6 already meets most requirements from this list. A library of potential nucleation inhibitors can readily be obtained by parallel synthesis (if not already commercially available). For instance, racemic family members of basic resolving agents can in general be prepared by relatively easy Leuckart[17] syntheses from the corresponding ketones (Scheme 7.6). One could even include family members of the substrate to be resolved in the screening process, according to the *reverse* Dutch Resolution protocol.



Scheme 7.6 *Synthesis of basic family members by Leuckart synthesis.*[17]

Because of the simplicity of the resolution process and its conditions, the requirements for robots are that they must be able to stir (or at least create effective vortex agitation), carry out gradual heating and cooling and be able to filtrate. Two machines that fit the requirements for a fully automated process are the Chemspeed's ASW 2000 (Figure 7.4*a*) and the Chemspeeds's Accelerator SLT 100 synthesizer (Figure 7.4*b*).[18]

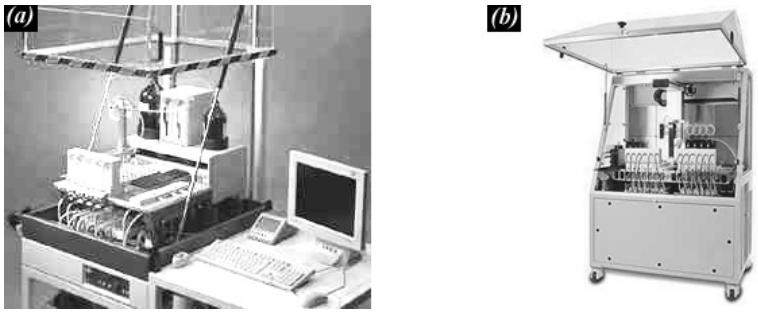
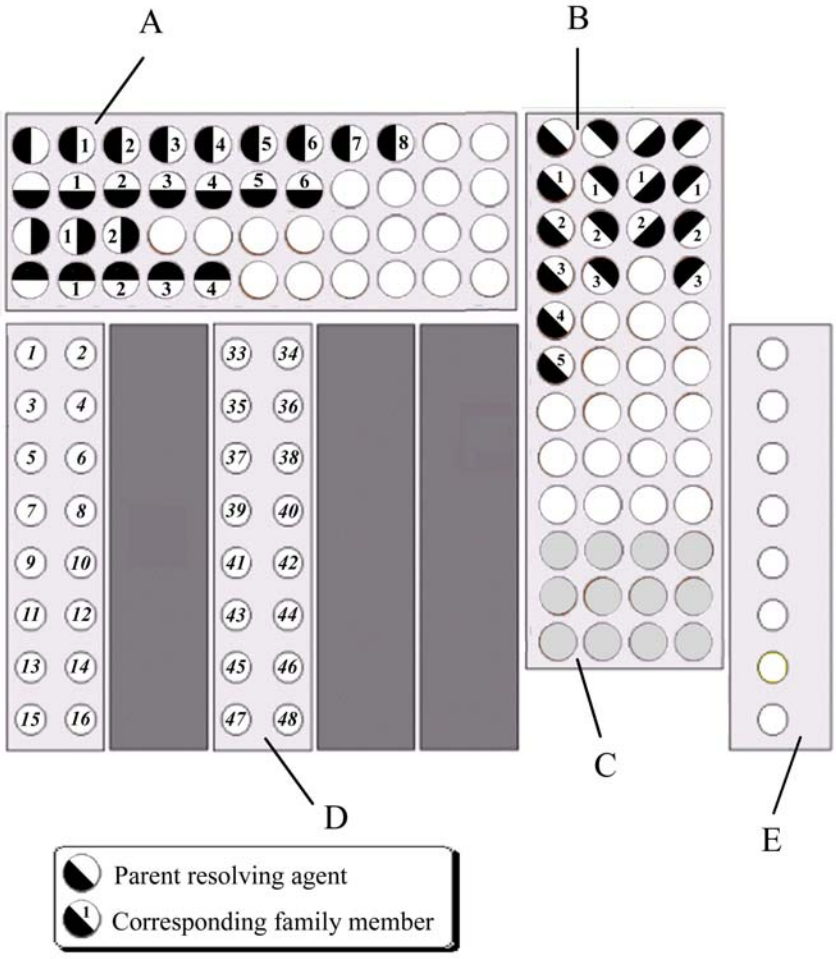


Figure 7.4 *The Chemspeed ASW 2000 (left) and the Accelerator SLT 100 (right).*

Both the ASW 2000 and the SLT 100 can hold up to 12 reaction blocks carrying up to 192 reactions in parallel. A fictitious experimental set-up is depicted in Figure 7.5.



A Stock solutions with basic resolving agents and family members

B Stock solutions with acidic resolving agents and family members

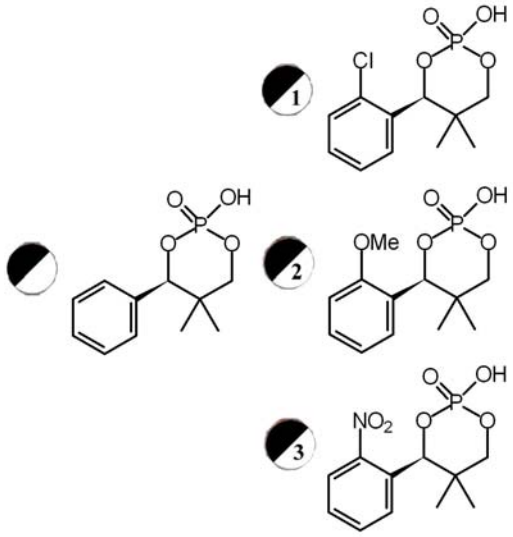
C Stock solutions of racemic substrates to be resolved

D Reaction block with reaction vessels

E Solvents

Figure 7.5 *Possible experimental set-up for the automated process in the Chemspeed robot.*

In Figure 7.5, the parent resolving agent is depicted as a coloured circle, ( ) and a family member of this parent is depicted as the same circle with a number. For instance, the family of four structurally related cyclic phosphoric acids that was used to resolve meta-nitro-phenylbutylamine **4.69** (Chapter 4.4 of this thesis) can be represented as:



Subsequently, all experiments can be analyzed by analytical chiral HPLC to measure the *de*'s. In principle, all parameters of the resolution experiments (S-factor, *de* and yield) can be determined from the mother liquor after filtration. Another possibility is to measure both the *de*'s of the mother liquor ($de_{\{ML\}}$) and of the first salts ($de_{\{salt\}}$) and process these raw data according to the following formula:

$$\text{Yield} = 100 \times \frac{de_{\{ML\}}(\%)}{de_{\{salt\}}(\%) + de_{\{ML\}}(\%)}$$

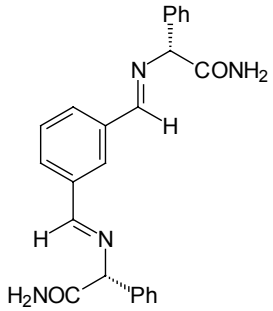
By carefully tuning the conditions of the HPLC-analysis, the ratio between the parent resolving agent and the additive in both the mother liquor and salt can be determined.

With the right mindset, it will just be a matter of time before for any desired substrate suitable conditions are found for resolution processes by performance of library screening of resolving agents.

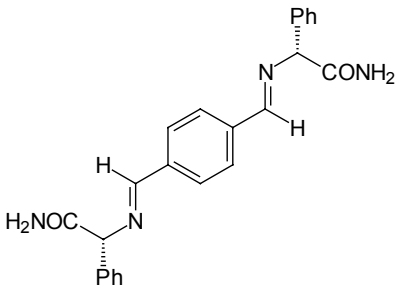
7.6 Experimental Section

General information: For general remarks concerning all experimental details see experimental section in Chapter 3. Conditions for resolution experiments and HPLC-analysis for each substrate are summarized in Chapter 6.9.

Procedure for the synthesis of diimines 7.11 and 7.12: The di-substituted benzaldehyde (100 mmol) was added to a suspension of (*R*)-phenylglycine amide (200 mmol, 30.0 g) in CH_2Cl_2 (200 mL) at ambient temperature. The reaction mixture was stirred overnight at room temperature. After removal of the CH_2Cl_2, the residual solid was recrystallized once from acetone/hexane (1:20).

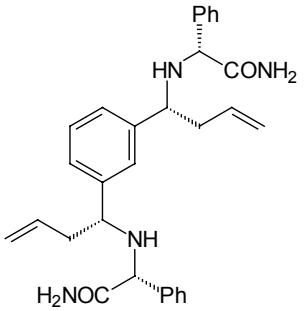


(2*R*)-2-({(*E*)-[3-({[(1*R*)-2-amino-2-oxo-1-phenylethyl]imino}methyl)phenyl]methylidene}amino)-2-phenylethanamide (7.11): (white solid, 96 % yield). m.p. 143.8–144.5 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 4.55 (s, 2H), 6.60 (brs, 2H), 6.63 (brs, 2H), 6.82–6.91 (m, 7H), 7.02–7.09 (m, 4H), 7.49 (d, J = 7.99 Hz, 2H), 7.79 (s, 1H), 7.94 (s, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 76.24 (d), 126.42 (d), 126.85 (d), 127.64 (d), 128.15 (d), 130.16 (d), 135.03 (s), 138.59 (s), 161.37 (d), 172.60 (s) ppm. Anal. Calcd. for $C_{24}H_{22}N_4O_2$: C, 72.34 %; H, 5.57 %; N, 14.06 %. Found: C, 72.21 %; H, 5.66 %; N, 14.03 %. MS (CI): m/z = 399 (M + H^+).

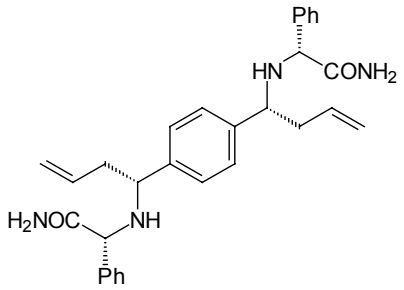


(2*R*)-2-({(*E*)-[4-({[(1*R*)-2-amino-2-oxo-1-phenylethyl]imino}methyl)phenyl]methylidene}amino)-2-phenylethanamide (7.12): (white solid, 98%) m.p. 168.1–168.3 °C. ^{1}H-NMR (300MHz, $CDCl_3$/[D_6]DMSO): δ = 4.53 (s, 2H), 6.58 (brs, 4H), 6.82–6.93 (m, 6H), 7.04 (dd, J = 8.42, J = 1.46 Hz, 4H), 7.45 (s, 4H), 7.93 (s, 2H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$/[D_6]DMSO): δ = 76.39 (d), 126.42 (d), 126.88 (d), 127.67 (d), 127.83 (d), 137.01 (s), 138.61 (s), 161.32 (d), 172.483 (s) ppm. Anal. calcd for $C_{24}H_{22}N_4O_2$: C, 72.34 %; H, 5.57 %; N, 14.06 %. Found: C, 71.95 %; H, 5.58 %; N, 13.87 %. MS (CI): m/z = 399 (M + H^+).

Procedure for the allylation of (*R*)-PGA diimines 7.11 and 7.12: A solution of allylzinc bromide (3.0 equiv.) was prepared by adding allyl bromide (25.7 mL, 292 mmol) to finely cut zinc wool (19.1 g, 292 mmol) in THF (150 mL). The solution of allylzinc bromide was cooled to room temperature and 97.3 mmol of the imine in THF (50 mL) was added at 0 °C. The reaction mixture was warmed to room temperature and then poured into water (100 mL). Ethyl acetate (70 mL) was added and the mixture was stirred vigorously. After filtration through Celite, the organic phase was separated and the water layer was extracted with ethyl acetate (2 × 100 mL). The combined organic phase was dried over sodium sulfate and the ethyl acetate was evaporated to furnish the PGA allylamines **7.14** or **7.15**, which in both cases crystallized on standing.



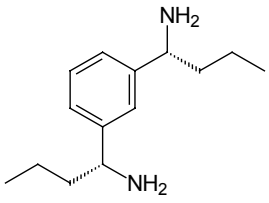
(2*R*)-2-({(1*R*)-1-[3-((1*R*)-1-{[(1*R*)-2-amino-2-oxo-1-phenylethyl]amino}-3-butenyl)phenyl]-3-butenyl}amino)-2-phenylethanamide (7.14): (yellow needles, 99 % yield, > 99:1 *dr*). m.p. 126.6–127.9 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.22 (brs, 2H), 2.36 (t, J = 6.59 Hz, 4H), 3.67 (t, J = 6.59 Hz, 2H), 3.94 (s, 2H), 4.97–5.03 (m, 4H), 5.59–5.72 (m, 2H), 6.58 (brs, 2H), 7.01–7.25 (m, 16H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.11 (t), 61.32 (d), 63.88 (d), 117.69 (t), 124.97 (d), 126.41 (d), 127.04 (d), 127.88 (d), 128.60 (d), 134.45 (d), 138.79 (s), 142.64 (s), 150.70 (d), 175.84 (s) ppm. Anal. calcd for $C_{30}H_{34}N_4O_2$: C, 74.66 %; H, 7.10 %; N, 11.61 %. Found: C, 74.66 %; H, 7.43 %; N, 11.53 %. MS (CI): *m/z* = 483 ($M + H^+$).



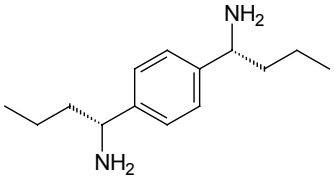
(2*R*)-2-({(1*R*)-1-[4-((1*R*)-1-{[(1*R*)-2-amino-2-oxo-1-phenylethyl]amino}-3-butenyl)phenyl]-3-butenyl}amino)-2-phenylethanamide (7.15): (pale yellow brittle solid, 99 % yield, > 99 % *dr*). m.p. 96.5–98.9 °C. ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.16-2.44 (m + brs, 5H), 3.70 (dt, J = 6.2 Hz, 2H), 4.05 (s, 2H), 4.95–5.10 (m, 4H), 5.61–5.69 (m, 2H), 6.26 (brs, 2H), 7.31–7.09 (m, 16H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 42.01 (d), 61.46 (d), 64.08 (d), 118.11 (t), 127.36 (d), 127.49 (d), 128.38 (d), 128.96 (d), 134.46 (d), 138.43 (s), 141.23 (s), 175.90 (s) ppm. Anal. calcd for $C_{30}H_{34}N_4O_2$: C, 74.66 %; H, 7.10 %; N, 11.61 %. Found: C, 74.70 %; H, 7.06 %; N, 11.62 %. MS (CI): *m/z* = 483 ($M + H^+$).

Procedure for the synthesis of diamino additives (*R*,*R*)-7.5 and (*R*,*R*)-7.6 by catalytic hydrogenation of PGA allylamines 48 and 49: The PGA allylamine (5.0 mmol) was dissolved in *i*–propylalcohol (50 mL). Water (50 mL), acetic acid (50 mL), and Pd–C (10 %) (0.4 gram, cat.) were added successively. After two vacuum/H_2 cycles to remove air from the reaction flask, the stirred mixture of the substrate was hydrogenated at ambient pressure of H_2 and room temperature for 5 days. After filtration, the *i*–propylalcohol was evaporated under reduced pressure. The residue was diluted with water (50 mL) and, while acidic, the reaction mixture was washed once with diethyl ether to remove any by-products. The aqueous phase was brought to pH 10 with 10% NaOH and was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phase was washed with brine, dried over sodium sulfate and filtered. After evaporation of the CH_2Cl_2, pentane was added to the residue. After filtration through a glass funnel, the pentane was removed under reduced pressure. Kugelrohr distillation yielded primary amines (*R*,*R*)-**7.5** and (*R*,*R*)-**7.6**.

1-{3-[(1*R*)-1-aminobutyl]phenyl}-1-butylamine (7.5): (colorless oil, 80 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.84 (t, J = 7.33 Hz, 6H), 1.11–1.34 (m, 4H), 1.52–1.61 (m + brs, 8H), 3.82 (t, J = 6.96 Hz, 2H), 7.11 (d, J = 7.69 Hz, 2H), 7.18 (s, 1H), 7.21 (t, J = 6.96 Hz, 1H) ppm. . ^{13}C-NMR (50MHz, $CDCl_3$): δ =13.96 (q), 19.70 (t), 41.84 (t), 55.97 (d), 124.22 (d), 124.69 (d), 128.38 (d), 155.35 (s) ppm. MS (CI): m/z = 441 [2M + H^+].



1-{4-[(1*R*)-1-aminobutyl]phenyl}-1-butylamine (7.6): (pale yellow oil, 74 % yield). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.75 (t, J = 7.33 Hz, 6H), 1.04–1.25 (m, 4H), 1.46–1.51 (m + brs, 8H), 3.70 (t, J = 6.78 Hz, 2H), 7.09 (s, 4H) ppm. ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.64 (q), 19.34 (t), 41.47 (t), 55.83 (d), 125.91 (d), 144.89 (s) ppm. MS (CI): m/z = 441 [2M + H^+].



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Nederlandse Samenvatting

De (organische) chemie heeft zo zijn eigen vakjargon. Om dit proefschrift enigszins begrijpelijk te maken voor niet-chemici is het nodig om 'de taal te spreken'. Deze Nederlandse samenvatting begint dan ook met een kleine, maar simpele uitleg over de taal die synthetisch chemici spreken. Na deze snelle taalcursus begint de samenvatting met een inleiding van de begrippen chiraliteit, enantiomeer en hun bioactiviteit. Dit proefschrift gaat voor het grootste gedeelte over het splitsen van enantiomeren via het "Dutch Resolution" protocol. Deze methode, die nog in de kinderschoenen staat van het toepassen en het begrijpen ervan, zal vergeleken worden met de "klassieke resolutie".

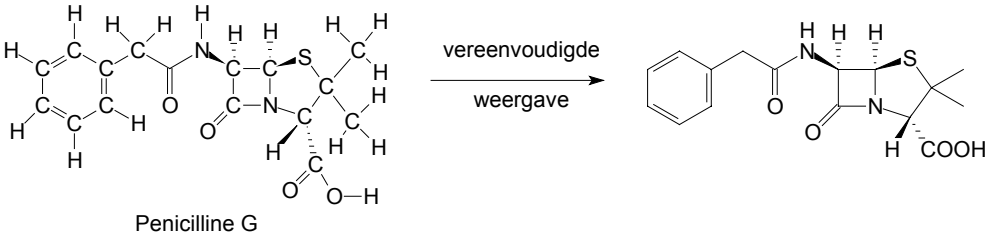
De Taal der Chemie

De chemie en het beschrijven van chemische experimenten kan worden gezien als (wereld)taal met zijn eigen taalgebruik. Alhoewel chemici liever hun werk uitdrukken in een voor de leek ingewikkeld uitziende formules en symbolen, is er wel degelijk een parallel te trekken met een 'normale' taal. Men moet de woorden en de grammatica kennen om een taal te spreken. Zoals een woord (molecuul) bestaat uit letters (atomen), zo bestaat een zin (reactiestap in een syntheseroute) uit woorden. Ieder atoom *c.q.* chemisch element wordt aangeduid met één of meer letters; de belangrijkste en meest gebruikte elementen in dit proefschrift zijn weergegeven in Tabel 1.

Tabel 1 *Chemische elementen en hun afkortingen.*

Element	Symbool	Element	Symbool
Broom	Br	Platina	Pt
Chloor	Cl	Waterstof	H
Koolstof	C	Zink	Zn
Stikstof	N	Zuurstof	O
Palladium	Pd	Zwavel	S

Om chemische tekeningen overzichtelijk te houden, worden niet alle atomen uitgeschreven wanneer men een molecuul tekent maar gebruikt men een soort van versimpelde weergave (steno). Een voorbeeld is weergegeven aan de hand van het Penicilline G-molecuul (Figuur 1). Hierin wordt elke chemische binding tussen de verschillende atomen weergegeven met verbindingsstreepjes, elke enkele bindingen met een "–", dubbele bindingen met een "=", en eventuele drievoudige bindingen met een "≡". Wanneer (groepen) atomen boven het vlak van papier staan, worden deze aangegeven met een "┃" en wanneer deze beneden het vlak van het papier staan, worden deze aangegeven met "┋".



Figuur 1 *Vereenvoudiging van de weergave van het antibioticum Penicilline G.*

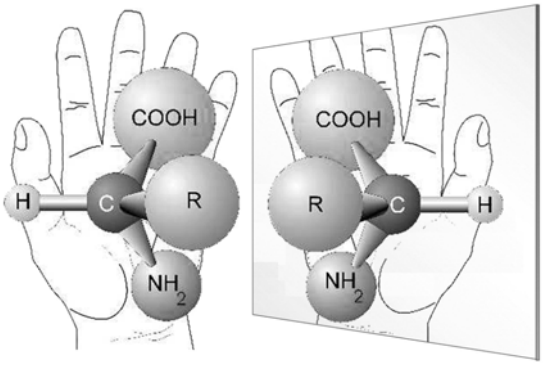
In de steno weergave worden een aantal vereenvoudigingen doorgevoerd:

- C-atomen worden veelal weggelaten en vervangen door een hoekpunt.
- Elk H-atoom dat op een C-atoom zit wordt meestal weggelaten. Wanneer deze zich op een "chiraal centrum" bevindt, laat men deze nog wel eens staan.
- Wanneer bepaalde atomen/groepen vaker gebonden zijn aan een atoom, worden deze nog wel eens afgekort door het aantal keren aan te geven dat deze gebonden is (*b.v.* –COOH wordt ook wel eens aangeduid als $-CO_2H$).
- Sommige groepen worden vervangen door een specifieke letternotatie, zoals de 6-ring aan de linkerkant van Penicilline G wordt nog wel eens vervangen door –Ph (afkomstig van Phenyl).

Een chiraal centrum is een koolstof atoom met vier verschillende bindingspartners, en wordt soms aangegeven met een "*"; Penicilline G bezit drie chirale centra. Chiraliteit is dusdanig belangrijk dat dit fenomeen behandeld zal worden in de volgende paragraaf.

Chiraliteit

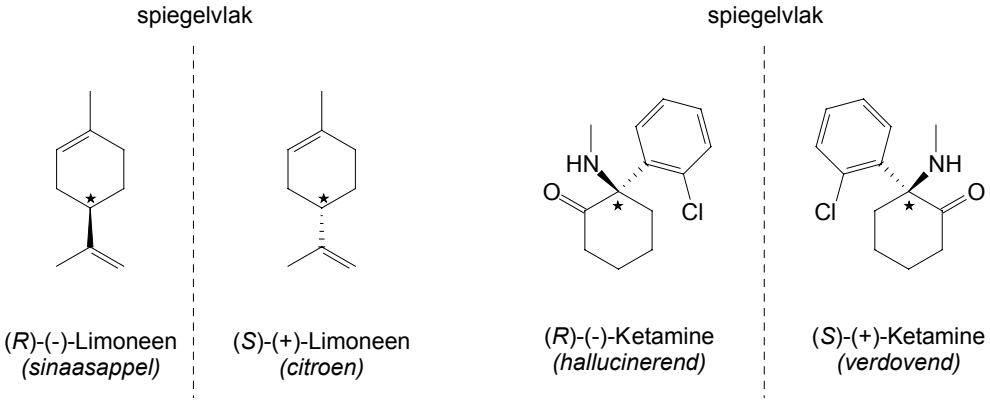
De Nederlandse scheikundige Jacobus Henricus van't Hoff is één van de grondleggers van de stereochemie. Van't Hoff opperde in 1874 dat moleculen niet plat waren maar driedimensionaal in de vorm van een tetraëder. Wanneer een centraal koolstofatoom zich in het midden bevindt en omringd is in de vorm van een tetraëder door 4 verschillende groepen, is er een spiegelbeeld mogelijk dat tot niet dekking te brengen is met het origineel (zoals een linker en een rechter hand, Figuur 2). Dit verschijnsel noemt men *chiraliteit*, naar het Griekse woord voor hand (Grieks; χειρ [cheir]). De studie van de verschillende spiegelbeeld-moleculen, de stereoisomeren, heet de stereochemie.



Figuur 2. *Moleculen of objecten die niet tot dekking gebracht kunnen worden met elkaar worden chiraal genoemd. Bovendien, alle aminozuren in het menselijk lichaam zijn "linkshandig".*

Chirale voorwerpen die we in onze allerdaagse omgeving aantreffen, zijn bijvoorbeeld schoenen, wenteltrappen, (scheeps)schroeven en misschien wel het meest illustratieve voorbeeld: onze handen. Zelfs in ons lichaam zijn alle aminozuren (behalve glycine) van elk eiwit 'linkshandig', terwijl alle suikers in DNA, RNA en in ons metabolisme 'rechtshandig' zijn.

De twee spiegelbeelden van een molecuul worden ook wel *enantiomeren* genoemd, en hebben veelal dezelfde (fysische) eigenschappen. De verschillen worden pas duidelijk wanneer deze enantiomeren in een chirale omgeving worden gebracht (ter illustratie, het is nagenoeg onmogelijk om een linkervoet in een rechterschoen te krijgen).



Figuur 3 *Enantiomeren van limoneen en ketamine en de bijbehorende bioactiviteit.*

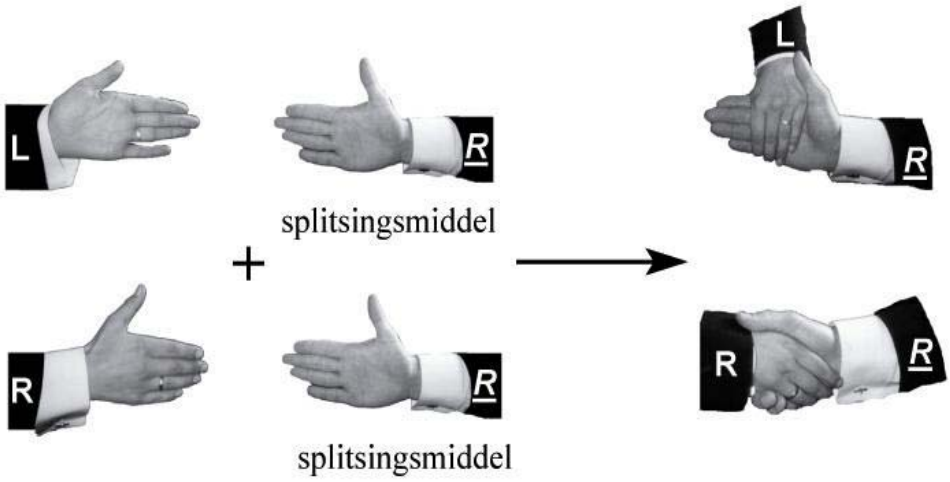
Enantiomeren kunnen een totaal andere werking hebben in het menselijk lichaam. Voorbeelden hiervan zijn de geur van limoneen en de werking van het medicijn ketamine (Figuur 3). De linksdraaiende vorm van limoneen ruikt naar sinaasappel en de rechtsdraaiende variant ruikt naar citroen. Een meer dramatisch voorbeeld is de werking van beide spiegelbeeldvormen van het narcosemiddel ketamine in ons lichaam. Het ene enantiomeer heeft de gewenste verdovende werking, terwijl het spiegelbeeld ervan een ongewenst hallucinerend effect heeft.

Deze verschillende bioactive werkingen illustreren meer dan eens het belang van het aanbieden van slechts één van de beide spiegelbeelden in bijvoorbeeld medicijnen. Wanneer men bij het uitvoeren van een chemisch experiment met achirale uitgangsstoffen begint, zal er zonder chirale invloed(en) een 1:1 mengsel onstaan van beide enantiomeren (*racemisch mengsel* of *racemaat*). Om deze reden is het belangrijk om een methode te hebben die deze spiegelbeeld vormen achteraf kan scheiden (splitsen).

Splitsingen

Spiegelbeeld-moleculen (enantiomeren) hebben veelal dezelfde fysische eigenschappen, zoals bijvoorbeeld hetzelfde kookpunt, smeltpunt of oplosbaarheid. Hierdoor is het niet mogelijk om enantiomeren van elkaar te scheiden door middel van conventionele technieken (b.v. destillatie).

Eén van de meest gebruikte benadering van het splitsen van beide enantiomeren wordt ook wel *klassieke resolutie* genoemd. Hierbij laat men het racemisch mengsel reageren met één enantiomeer van een **ander** molecuul (het *splitsingsmiddel*), zoals uitgebeeld is in Figuur 4. Zoals eerder genoemd bestaat een racemisch mengsel uit een 1:1 mengel van beide spiegelbeelden (weergegeven als handen L en R). Door deze in contact te brengen met een splitsingsmiddel dat bijvoorbeeld uitsluitend uit 'rechterhanden' (*R*) bestaat, ontstaan twee *diastereomeren* (L*R* en R*R*) waartussen geen spiegelbeeld relatie meer bestaat. Hiertoe worden in de praktijk alle componenten bij elkaar gedaan en verwarmd tot een heldere oplossing is verkregen waarna het gehele mengsel langzaam afgekoeld wordt. Omdat na reactie in de diastereomeren de onderlinge spiegelbeeld-relatie opgeheven is, kunnen deze nu wél gescheiden worden door conventionele technieken.



Figuur 4 *Het splitsen van spiegelbeelden (enantiomeren) door een splitsingsmiddel te gebruiken (klassieke resolutie).*[1]

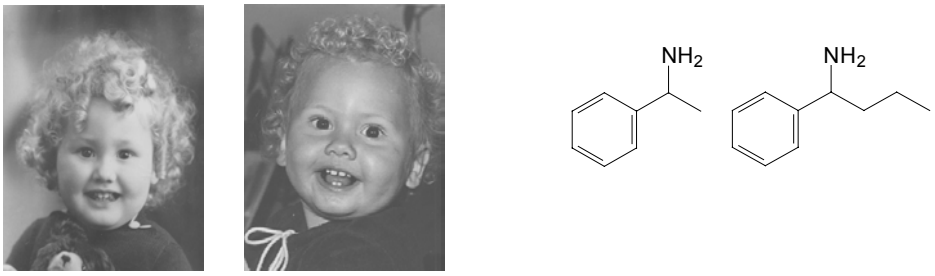
[1] Dr. I. Visscher en Dr. M. K. J. Ter Wiel worden hartelijk bedankt voor het meewerken aan deze illustratieve foto's.

In klassieke resolutie worden twee diastereomere zouten gevormd, die verschillen in hun onderlinge oplosbaarheid in een bepaald oplosmiddel. Het ene diastereomere zout zal goed oplosbaar zijn in het gekozen oplosmiddel en na afkoelen (grotendeels) in oplossing blijven, terwijl het slecht oplosbare diastereomere zout bij afkoelen bij een bepaalde temperatuur zal uitkristalliseren (er treedt *nucleatie* op). Wanneer dit is gebeurd, kunnen de twee diastereomeren door filtratie simpelweg gescheiden worden. Nadat men het mengsel weer ontdaan heeft van het splitsingsmiddel, is het splitsen van de enatiomeren voltooid.

Deze methode is sinds de ontdekking in 1847 door Louis Pasteur weinig veranderd qua techniek. Het is op de dag van vandaag de meest gebruikte methode in de industrie in de productie van enantiomeer zuivere preparaten.

Dutch Resolution

In 1998 werd een variant op deze “klassieke resolutie” ontwikkeld in Groningen. Deze methode maakt geen gebruik van één splitsingsmiddel, maar van een mengsel van twee of drie sterk op elkaar lijkende - een “familie” van - splitsingsmiddelen. Deze nieuwe variant staat nu bekend als *Dutch Resolution*.



Figuur 5 *Twee familieleden die onderling sterk op elkaar lijken qua (a) gezichts-structuur of (b) chemische structuur.*

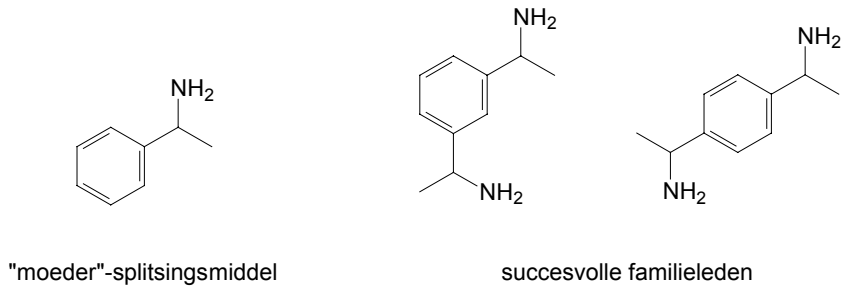
Bij het doorontwikkelen van deze nieuwe methode kwam men erachter dat één van de familieleden **niet** voorkwam in het gekristalliseerde zout maar **wel** de efficiëntie van de splitsing ten goede kwam. Het vermoeden rees dat dit niet-ingebouwde familielid het nucleatieproces bij afkoelen in ons voordeel beïnvloedt, waarbij het goed oplosbare zout min of meer gedwongen wordt nog langer in oplossing te blijven (inhibitie van nucleatie). In deze doorontwikkelde variant, die we de ‘tweede generatie’ noemen (second generation Dutch Resolution), is er slechts een kleine hoeveelheid (< 10 %) van dit niet-ingebouwde familielid nodig (*nucleation inhibitor*) in een splitsingsproces.

Dit Proefschrift

Het onderzoek dat in dit proefschrift beschreven wordt, is zeer divers. Het eerste doel was het vervaardigen van een nieuwe potentiële familie van splitsingsmiddelen (hoofdstukken 3 en 4). Deze verbindingen zijn niet alleen nuttig in splitsings-experimenten, maar kunnen ook belangrijke bouwstenen zijn in de synthese van farmaceutisch interessante verbindingen zoals bijvoorbeeld β-aminozuren en antibiotica.

Het testen van deze potentiële nucleatie inhibitoren volgens het 'second generation Dutch Resolution'-protocol wordt besproken in hoofdstuk 5 en 6. In hoofdstuk 6 worden ook andere moleculen, variërend in structuur, getest om meer inzicht te krijgen in wat nu de (structurele) relatie tussen onderlinge familieleden is. Tijdens het testen kwamen er twee belangrijke aspecten aan het licht; ten eerste bleek een snellere screeningsmethode mogelijk door na het experiment direct de zouten te analyseren. Ten tweede bleek het mogelijk om racemische additieven te screenen; deze racemische additiven zijn (synthetisch) makkelijker toegankelijk en vaak ook commercieel verkrijgbaar. Aangezien vervolg-experimenten altijd gebaseerd moeten worden op voorgaande analyses, versnelt dit het tijdrovende verkrijgen van resultaten (en dus inzicht) aanzienlijk.

Bij het screenen, waren er twee familieleden die de efficiënties van de splitsingen wel een factor 2 tot 3 verbeterden. Opvallend feit hierbij was dat deze additieven niet één maar twee amino-groepen (–NH_2) bezitten in hun structuur (Figuur 6).



Figuur 6 *Het "moeder"-splitsingsmiddel en haar twee meest succesvolle familieleden uit hoofdstuk 6*

Deze waarneming heeft geleid tot de synthese van de verbindingen die beschreven wordt in hoofdstuk 7. Deze nieuwe klasse van verbindingen kon gesynthetiseerd worden aan de hand van dezelfde elegante methode die we gebruikt hebben voor het vervaardigen van de verbindingen in hoofdstuk 3 en 4.

Stellingen

Behorende bij het proefschrift van

Jan Dalmolen

[1] Voor de synthese van moleculen geldt: beter een lage opbrengst dan helemaal niet te maken.

[2] Dat men het vak van promovendus vaak niet serieus neemt, blijkt wel wanneer ze zeggen: ”Als je later een *echte* baan hebt....”.

[3] De meeste niet-wetenschappelijke stellingen in proefschriften ontstaan vaak in de laatste maanden van een promotie uit pure frustratie.

[4] De opvang in zogenaamde slaaphuizen voor daklozen en zwervers zou gratis moeten worden.

[5] Aangezien de activiteit van elk commercieel verkrijgbaar potje palladium op kool verschillend is, zou moeten gelden: “Niet goed, geld terug”.

[6] Stille tochten leiden niet tot rust op straat.

[7] Het automatisch ontgrendelen van autoportieren via de autosleutel, gepaard gaande met geluidssignalen en geknipper van autolampen om aan te geven waar een auto zich bevindt op bijvoorbeeld een overvol parkeerterrein, is niet alleen gemakkelijk voor de desbetreffende eigenaar maar ook voor potentiële autodieven.

[8] Het gedoogbeleid van onderzoeksinstituten om AIO’s en postdocs de vrijheid te geven om af te wijken van de “half-negen-tot-vijf-mentaliteit” en hun werktijden op labzalen zelf maar in te delen, leidt tot gevaarlijke situaties.

[9] Een langere aanwezigheid op de werkplek hoeft niet per definitie te leiden tot een verhoogde productiviteit.

[10] Het beschikbaar stellen van een pc voor het schrijven van een proefschrift tegen het eind van een promotieonderzoek is als mosterd na de maaltijd. Veel efficienter is elke promovendus aan het *begin* van hun onderzoek te voorzien van een computer (bij voorkeur een laptop).

[11] De opmerking dat regioselectiviteit in competitative debenzyleringsreacties “has not been fully investigated *until now*”, om vervolgens naar het effect op de selectiviteit van maar één substituent te kijken, is ronduit voorbarig en kortzichtig.

M. Kanai et al., *Org. Lett.* **2003**, *7*, 1007–1010.

[12] De veel gebruikte uitdrukking dat het uitvoeren van splitsingen meer een kunst is dan wetenschap (“resolutions are art rather than science”), doet vermoeden dat onderzoekers die zich op dit vakgebied begeven eerder kunstenaars zijn dan wetenschappers.

[13] Het is aannemelijk dat (second generation) “Dutch Resolution” voortkomt uit “French Resolution”.

Zie dit proefschrift.